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- (4) Novel 7-substituted-9-substituted amino-6-demethyl-6-deoxytetracyclines.
- Novel 7-substituted-9-(substituted amino)-6-demethyl-6-deoxytetracycline compounds having activity against a wide spectrum of organisms including organisms which are resistant to letracyclines are disclosed. Also disclosed are intermediates and methods for making the novel compounds of the present invention.

# BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

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The invention relates to novel [45-(4.12aa)]+-(dimethylamino)-7-(substituted)-9-(substituted amino)-1.4.4a,5.5a,6.11.12a-ctalhydro-3.10.12.12a-teriany/dxoy-1.1-i-dixxo-2-naphthacenecarboxamides hereinatter called 7-(substituted)-9-(substituted amino)-6-demethyl-8-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to letracyclines and are useful as antibiotic agents. The invention also relates to novel 7-(substituted)-9-(substituted amino)-6to demethyl-6-deoxytetracycline intermediates useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

#### DESCRIPTION OF THE PRIOR ART

A variety of tetracycline antibiotics have been synthesized and described for the treatment of infectious diseases in man and animals since 1947. Tetracyclines inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome preventing binding of aminoacyl RNA (Chopra, Handbook of Experimental Pharmacology, Vol. 78, 317-392, Springer-Verlag, 1985). Resistance to tetracyclines has emerged among many clinically important microorganisms which limit the utility of these antibiotics. There are two major 20 mechanisms of bacterial resistance to tetracyclines; a) energy-dependent efflux of the antibiotic mediated by proteins located in the cytoplasmic membrane which prevents intracellular accumulation of tetracycline (S. B. Levy, et al., Antimicrob. Agents Chemotherapy 33, 1373-1374 (1989); and b) ribosomal protection mediated by a cytoplasmic protein which interacts with the ribosome such that tetracycline no longer binds or inhibits protein synthesis (A. A. Salvers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156, 25 1990). The efflux mechanism of resistance is encoded by resistance determinants designated tetA-tetL. They are common in many Gram-negative bacteria (resistance genes Class A-E), such as Enterobacteriaceae, Pseudomonas, Haemophilus and Aeromonas, and in Gram-positive bacteria (resistance genes Class K and L), such as Staphylococcus, Bacillus and Streptococcus. The ribosomal protection mechanism of resistance is encoded by resistance determinants designated TetM, N and O, and is common in 30 Staphylococcus, Streptococcus, Campylobacter, Gardnerella, Haemophilus and Mycoplasma (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156 1990).

A particularly useful totracycline compound is 7-(dimethylamino)-B-demethyl-B-deoxytetracycline, known as minocycline (see U.S. 3,148,212, RE 28,253 and 3,226,436 discussed below). However, strains harboring the tetB (efflux in gram-negative bacteria) mechanism, but not tetK (efflux in Staphylococcus) are resistant so minocycline. Also, strains carrying tetM (ribosomal protection) are resistant for minocycline. This invention describes the synthesis of novel tetracycline compounds which demonstrate significant in vitor and in vivo activity vs. tetracycline and minocycline susceptible strains and some tetracycline and minocycline resistant strains, that is, those harboring the tetM (ribosomal protection) resistance determinants.

Duggar, U.S. Patent No. 2,482,055, discloses the preparation of Aureomycin® (I) by fermentation which on have antibacterial activity. Growich et al., U.S. Patent No. 3,007,965, disclose improvements to the fermentation preparation of I. Neither of these patents teaches or suggests the 6-demethyl-6-deox-vietracyclines.

ss Beereboom et al., U.S. Patent No. 3,043,875 discloses tetracycline derivatives of the formulae (II) and (III) where R is H or Cht; R: is H and when R is Cht, OH; R<sub>2</sub> is H and NICH<sub>3/2</sub>: X and Y are halogen: Z is H and halogen and B is bromo, chloro and iodo, which have antibacterial activity. This patent does not teach or suggest the inclusion of both di[lower alkyl]amino or monot(lower alkyl]amino substituents (at Y or Z) and

an amino function (at B).

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Boothe et al., U. S. Patent No. 3,148,212, reissued as RE26,253, and Petisi et al., U.S. Patent No. 3,226,436, discloses tetracycline derivatives of the formula (IV) wherein R is hydrogen or methyl and R<sub>1</sub> and 15 R<sub>2</sub> is hydrogen, mono(lower alkyl)amino or di(lower alkyl)amino with the proviso that R<sub>1</sub> and R<sub>2</sub> cannot both be hydrogen, which are useful for treating bacterial infections. This patent does not teach or suggest the inclusion of a 9-amino functionality (at R<sub>2</sub>).

Blackwood et al., U.S. Patent No. 3,200,149 discloses tetracycline derivatives of the formulae (V) and (VI) 30 and reduction products thereof wherein Y may be hydrogen or hydroxyl, X may be hydrogen, chloro, lodo, or bromo, X, may be hydrogen, amino, and lower alkanoylamino, X<sub>2</sub> may be hydrogen or nitro and Z is chloro or fluoro which possess microbiological activity. This patent does not teach or suggest the inclusion of both a di(lower alkyl)amino group (at X) and another nitrogen functionality (at X<sub>1</sub>) on the 6-demethyl-6deoxyldracycline nucleus.

Petisi et al., U.S. Patent No. 3,338,963 discloses tetracycline compounds of the formula (VII) wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen, nitro, amino, formylamino acetylamino, po-(aminobenzonesulfonylamino, chlorine, bromine or diazonium with the proviso that R<sub>1</sub> and R<sub>2</sub> may not both be hydrogen and with the further proviso that when R<sub>1</sub> is chlorine or bromine, R<sub>2</sub> may not be hydrogen and viice versa, R<sub>2</sub> is hydrogen or methyl and R<sub>1</sub> is hydrogen or hydroy, which have broad-spectrum antibacterial activity. This patent does not teach or suggest the inclusion of both di(lower alkyl)amino or monoflower alkyllamino subtiliuents (at R<sub>2</sub>), and amino substituents (at R<sub>2</sub>).

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**V** ( )

Bitha et al., U.S. Patent No. 3,341,856 discloses tetracycline compounds of the formula (VIII) wherein R<sub>i</sub> is a-methyl or β-methyl, and R<sub>V</sub> and R<sub>V</sub> and R<sub>V</sub> are each hydrogen, mono-(lower alkyl)amino or di(lower alky)lamino with the proviso that R<sub>V</sub> and R<sub>V</sub> cannot both be hydrogen and with to the further proviso that when R<sub>V</sub> is hydrogen then R<sub>V</sub> is α-methyl. A preferred embodiment of the general formula (VIII) is when R<sub>V</sub> is α-hydroxy, R<sub>V</sub> is α-methyl. A preferred embodiment of the general formula (VIII) is when R<sub>V</sub> is α-hydroxy, R<sub>V</sub> is α-methyl or methyl. R<sub>V</sub> is di(lower alkyl)amino and R<sub>V</sub> is hydrogen, which have broad-spectrum antibacterial activity. This patent does not teach or suggest the inclusion of both di(lower alkyl)amino or mono(lower alkyl)amino substituents (at R<sub>V</sub>) and amino substituents (at R<sub>V</sub>).

V 1 1 1

Shu, U.S. Patent No. 3,360,557 discloses 9-hydroxytetracyclines of the formula (IX) wherein R, is hydrogen or hydroxy, R, E is hydrogen or hydroxy, R is hydrogen or hydroxy, R is hydrogen or methyl. R, and R, taken together is methylene, and R is hydrogen, halogen, nitro, amino, mono(lower alkyl)amino or di(lower alkyl)amino, which have been se found to possess antibacterial activity. This patent is restricted to 9-hydroxytetracyclines and does not teach or suggest the presently claimed compounds.

ΙX

Zambrano, U.S. Patent No. 3,360,561 discloses a process for preparing 9-nitroteracyclines of the formula (X) wherein R<sub>8</sub> is hydrogen or hydrow, R<sub>1</sub> is is hydrogen or hydrow, R<sub>1</sub>, et al., taken together is methylene, R<sub>7</sub> is hydrogen, chloro or nitro and R<sub>1</sub> is hydrogen or nitro with the proviso that R<sub>7</sub> and R<sub>8</sub> cannot both be hydrogen. This patent does not beach or suggest the inclusion of both a di50 (lower alkylpamino or monolywer alkylpamino substituent (are R<sub>7</sub>) and an amino functionality (af R<sub>9</sub>).

X

Martell et al., U.S. Patent No. 3,518,306 discloses 7-and/or 9-(N-nitrosoalkylamino)-6-demethyl-6-deoxytetracyclines of the formula (XI) which possess in vivo antibacterial activity. This patent does not teach or suggest the inclusion of both a dil(lower alkyl)amino or mono(lower alkyl)amino substituent (at C-7) and an amino functionality (at C-9).

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In U.S. 5,021,407, a method of overcoming the resistance of tetracycline resistant bacteria is disclosed.

The method involves utilizing a blocking agent compound in conjunction with a tetracycline type antibiotic.

This patent does not disclose novel tetracycline compounds which themselves have activity against resistant organisms.

In summary, none of the above patents teach or suggest the novel compounds of this application. In addition, none of the above patents teach or suggest novel tetracycline compounds having activity against a tetracycline and minocycline resistant strains as well as strains which are normally susceptible to tetracyclines.

# SUMMARY OF THE INVENTION

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This invention is concerned with novel 7-(substituted)-9-(substituted amino)-6-demethyl-6-deoxytetracyclines, represented by formula I and II, which have antibacterial activity; with method of treating infloctious diseases in warm blooded animals employing these new compound; with methods of treating or controlling veterinary diseases; with pharmaceutical preparations containing these compounds; with novel intermediate compounds and processes for the production of these compounds. More particularly, sits invention is concerned with compounds of formula I and II which have enhanced in vitro and in vivo antibiotic activity against tetracycline resistant strains as well as a high level of activity against strains which are normally susceptible to stracyclines.

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In formula I and II, X is selected from amino, NR1R2 or halogen; the halogen is selected from bromine, 25 chlorine, fluorine or iodine;

and when X = NR1R2 and R1 = hydrogen,

R2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R1 = methyl or ethyl,

R2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

30 and when R1 = n-propyl,

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R<sup>2</sup> = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R1 = 1-methylethyl.

R2 = n-butyl, 1-methylpropyl or 2-methylpropyl; and when R1 = n-butyl.

35 R2 = n-butyl, 1-methylpropyl or 2-methylpropyl; and when R1 = 1-methylpropyl.

 $R^2 = 2$ -methylpropyl:

R is selected from R<sup>t</sup> (CH<sub>2</sub>)<sub>n</sub>CO- or R<sup>d'</sup> (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-; and when R = R<sup>t</sup> (CH<sub>2</sub>)<sub>n</sub>CO- and n = 0. R4 is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C1-C6)-

40 alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C1-C4)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1dimethylethyl; (C3-C6)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; 45 substituted (C3-C5)cycloalkyl group (substitution selected from (C1-C3)alkyl, cyano, amino or (C1-C3)acyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C9)aralkyl group selected from benzyl, 1-phenylethyl, 2phenylethyl or phenylpropyl; α-amino(C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from aminomethyl, α-aminoethyl, α-50 aminopropyl or α-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, αaminobutyric acid or α-aminopropionic acid and their optical isomers; (C7-C9)aralkylamino group such as phenylglycyl; (C1-C4)alkoxycarbonylamino substituted (C1-C4)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C1-C3)alkyl group selected from hydroxymethyl, α-hydroxyethyl or αhydroxy-1-methylethyl or  $\alpha$ -hydroxypropyl;  $\alpha$ -mercapto( $C_1$ - $C_3$ )alkyl group selected from mercaptomethyl,  $\alpha$ -55 mercaptoethyl, α-mercapto-1-methylethyl or α-mercaptopropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl or 2-iodoethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a

benzo or pyrido ring fused thereto:

#### Z = N. O. S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofthianyl, thianyl, benzofuranyl, tetrahydrofthianyl, thianyl, benzofuranyl, tetrahydrofthianyl, thianyl, benzofuranyl, benzofuranyl, benzofuranyl, tetrahydrofthianyl, benzofuranyl, b

ring fused thereto:

## Z or $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol(4,5-b]pyridyl or pyridylimidazoly, or a live membered saturated ring with one or two N, O, S or Se helbroatoms and an adjacent appended O heteroatom:

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(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxyl; (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, t-phenylethyl, 2-phenylethyl or phenyl-propull

such as -butyrolactam, -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatoms such as pyridyl, pyridazinyl, symthazinyl, usymthazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-totyl-2,3-dioxo-1-piperazinyl, 4-totyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothomorpholinyl; acyl or halioacyl group selected from acetyl, propionyl, chloroacetyl, tiftluoroacetyl, (10,-ck.)cycloalkylcarbonyl such as cyclopropylcarbonyl, cyclobutyl-carbonyl, cyclopropylcarbonyl, (2-dithylcyclopropylcarbonyl, (12-dithylcyclopropylcarbonyl, (12-dithylcyclopropylcarbonyl), (12-dithylcyclopropylcarbonyl, (12-dithylcyclo

pyrido ring fused thereto:

Z = N, O, S or Se

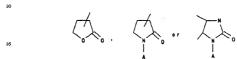
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

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such as limidazolyl, pyrazolyl; benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, ithiazolyl, benzothiazolyl, 3alakyl-3H-limidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:



40 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>1</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoyycarbonyl, (C<sub>1</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylerpovyl

such as -p-butyrolactam, -p-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered sa aromatic ring with one to three N. O. S or Se heteroatoms such as pyridy, pyridazinyi, pyradriazinyi, byradriazinyi, byradriazinyi, byradriazinyi, byradriazinyi, byradriazinyi, and the property of the property o

Z = N, O, S or Se

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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrollidinyl, 3-pyrrollidinyl, 2-pyrrollinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofthienyl, thienyl, benzofthienyl or selenazolyl):

10 (Ci-Cl-) alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or tent-butoxy; Ci-anyloxy group selected from phane, (Ci-Cl<sub>2</sub>) alky, Initin, cyano, thiol, amino, carboxy, di(Ci-C<sub>2</sub>) alky, Iamino); (Ci-Cl<sub>2</sub>) alkyloxy group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; vinyloxy or substituted vinyloxy group (substitution selected from (Ci-Cl<sub>2</sub>) alkyloxy group, selected from phenyl, α-naphtylor σ'.β-naphtyl); RPPamino(Ci-Cl<sub>2</sub>) alkyloxy group, wherein RPPs is a straight or branched (Ci-Cl<sub>2</sub>) alkyl selected from methyl, ethyl, n-propyl, 1-methyloythyl, n-butyl, 1-methylorpoyl, 2-methylorpoyl or 1,1-dimethylothyl or RPPs is (Ci+D<sub>2</sub>), n-2-6, σ'.(Ci+D<sub>2</sub>) wl(Ci+D<sub>2</sub>) alkyl (straight or branched]. NH, -NOB (B is selected from NHC), 0-0 or Si or RPP aminoxy group, wherein RPPs is Ci+D<sub>2</sub> alkyl selected from tentyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPh is (Ci+D<sub>2</sub>), n-2-6, or -(Ci+D<sub>2</sub>) wl(Ci+D<sub>2</sub>) awherein W is selected from NHCn-C<sub>3</sub>) alkyl glataght or branched]. NH, -NOB (B is selected from nethyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPh is (Ci+D<sub>3</sub>), n-2-8, or -(Ci+D<sub>2</sub>) wl(Ci+D<sub>2</sub>) awherein W is selected from NHCn-C<sub>3</sub>) alkyl glataght or branched]. NH, -NOB (B is selected from nethyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or 2-methylpropyl or 2-methylpropyl or 2-methylpropyl or 2-methylpropyl, n-10-10 alkyl glataght or branched]. NH, -NOB (B is selected from nethyl) are not not necessary and necessary and necessary are not necessary and necessary and necessary and necessary and necessary and necessary are necessary and necessar

and when  $R = R^4(CH_2)_nCO$ - and n = 1-4,

R¹ is selected from hydrogen; amino; straight or branched (G;-G\_alkyl group selected from methyl, ethyl, n-propyl, 1-methylerbyl, n-bropyl, 1-methylerbyl, n-bropyl, 1-methylerbyl, n-bropyl, 1-methylerbyl, (G\_c-G\_c)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (G\_c-G\_c)cycloalkyl group (substitution selected from (G;-G\_alkyl, cyano, amino or (G;-G\_alcyl); (G\_c-G\_a)ayl group selected from phonyl, -naphthyl or β-anphthyl; substituted(G\_c-G\_alva)rgoup (substitution selected from halo, (G;-G\_alva) arkayl group selected from benzyl, -for-brounded(G\_c-G\_alva)rgoup (substitution selected from halo, (G;-G\_alva)rgoup), (G;-G\_alkyl, group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl or carboxyl, (G;-G\_alva)rgov), rehalosopylogy group, selected from acetyl, propionyl, chloroacetyl, trichloroacetyl, (G;-G\_c)cycloalkylcarbonyl, (G;-G\_c)aroyl selected from benzoyl or aphthyl, halo substituted (G;-G;alkylbenzoyl) selected selected from selected from benzoyl or 3,4-dilutochenzoyl, G;-G\_alkylbenzoyl selected selected from selected f

· ·

Z = N, O, S or Se

45 such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

## Z or $Z^1 = N$ , O, S or Se

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such as imidazolyl, pyrracolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, ithiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-blpyridyl or pyrdyl midazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

15 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-proov)!

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered 20 aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxy group such as allyloxy, methoxy, 25 ethoxy, n-propoxy,n-butoxy or tert-butoxy; C6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); (C<sub>7</sub>-C10) aralkyloxy group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; (C1-C3) alkylthio group selected from methylthio, ethylthio, propylthio or allylthio; C6-arylthio group selected from phenylthio or substituted phenylthic (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di-30 (C<sub>1</sub>-C<sub>3</sub>)alkylamino); C<sub>6</sub>-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C8)aralkylthio group such as benzylthio, 1-phenylethylthio or 2-phenylethylthio; a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

# Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

# $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-

alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution 15 selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoyycarbonyl, (C<sub>1</sub>-C<sub>5</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O,S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-20 triazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; hydroxy group; mercapto group; mono- or distraight or branched chain (C1-C6)alkylamino group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-25 butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylpropyl, 1,1-dimethylpropyl, 2,2dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl or 1-methyl-1-ethylpropylamino; (C2-C5)azacycloalkyl group such as aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or 2-methylpyrrolidinyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, a-aminopropionic acid, a-aminoputyric acid and their optical isomers: 30 α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy-1-methylethyl or αhydroxypropyl; halo(C1-C3)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2-trifluoromethyl, 2bromoethyl or 2-iodoethyl; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, trifluoroacetyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkylcarbonyl, (C<sub>6</sub>-C<sub>10</sub>)-aroyl selected from benzoyl or naphthoyl, halo substi-35 tuted (C<sub>6</sub>-C<sub>10</sub>)aroyl such as pentafluorobenzoyl, 4-chlorobenzoyl, 3-bromobenzoyl, 3,4-difluorobenzoyl, (C<sub>1</sub>-C4) alkylbenzoyl such as 4-tolucyl, 2-tolucyl or 4-(1-methylethyl)benzoyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

se such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidnyl, 3-pyrrolidnyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl,benzofuranyl, tetrahydrofthienyl, thienyl, benzofutenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyridor ing fused thereto:

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Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3to alkyl-3H-imidazol4,5-b]pyridyl or pyrdylimidazolyl, or a live membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with 30 one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxvcarbonylamino: (C1-C4)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched butoxycarbonyl; RaPamino(Ci-Cu)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or R3Rb aminoxy group, wherein R3Rb is a straight or branched (C1-C4)alkyl 40 selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; and when  $R = R^4 (CH_2)_n SO_2$ - and n = 0,

Ff is selected from amino: monoscubstituted amino selected from straight or branched (C--C<sub>a</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylylamino) or phenylamino, disubstituted amino selected from dimethylamino, diethylamino, piperdidnyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-fl.(2-3-frazolyl) or 4-(1,2-4-frazolyl); straight or branched (C--C<sub>a</sub>)akyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 2-methylpropyl or 1-yl-dimethylethyl, (C<sub>a</sub>-C<sub>a</sub>)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclobacyl; so substituted (C<sub>3</sub>-C<sub>a</sub>)cycloalkyl group selected from (C<sub>1</sub>-C<sub>a</sub>)akyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>a</sub>-C<sub>1</sub>-c)aryl group selected from phanyl, α-maphtyl or β-maphthyl; substituted (C<sub>2</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, (C<sub>3</sub>-C<sub>a</sub>)cyclopropyl, halof(C<sub>3</sub>-C<sub>a</sub>)alkyl, group such as bornyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; halof(C<sub>3</sub>-C<sub>a</sub>)alkyl group such as bornyl, 1-phenylethyl, 2-phenylethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-2-dichloromethyl, 2-2-dichl



## Z = N, O, S or Se

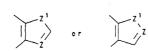
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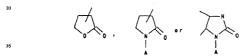
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such as pyrrolyl, N-methylindolyl, Indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofurinyl, thienyl, benzofurinyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



## Z or $Z^1 = N, O, S$ or Se

28 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl, 5-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution 49 selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenyleithyl, 2-phenylethyl or phenylpropyl)

such as  $\gamma$ -bulyrolactam,  $\gamma$ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered armatic ring with one to three N. O. S or Se heteroatoms such as pyridy, pyridazinyl, pyraidnyl, syriadinyl, pyraidnyl, pyrai

# and when R = R4 CH2), SO2- and n = 1-4.

R<sup>4\*</sup> is selected from hydrogen; amino; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; (C<sub>1</sub>-C<sub>4</sub>)carboxyalkyl

group; (C3-C6)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C1-C3)alkyl, cyano, amino or (C1-C3)acyl); (C6-C10)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino 5 or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; (C₁-C<sub>6</sub>)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy or tert-butoxy; C<sub>6</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C1-C2)alkyl, nitro, cyano, thiol, amino, carboxy, di(C1-C3) alkylamino); (C7-C10) aralkyloxy group such as benzyloxy, 1-phenylethyloxy or 2phenylethyloxy; RaRb amino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is  $(CH_2)_n$ , n = 2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_2)$ alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or R3R5aminoxy group, wherein R3R5 is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)a, n = 2-6, or -(CH2)2W(CH2)2- wherein W is selected from -N(C1-15 C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; (C<sub>1</sub>-C<sub>3</sub>)alkylthio group selected from methylthio, ethylthio or n-propylthio; C6-arylthio group selected from phenylthio or substituted phenylthio (substitution selected from halo, (C1-C3)alkyl, nitro, cyano, thiol, amino, carboxy, di(C1-C3)alkylamino); (C7-C8)aralkylthio group such as benzylthio, 1-phenylethylthio or 2phenylethylthio; a heterocycle group selected from a five membered aromatic or saturated ring with one N, 20 O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

## Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furranyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazotyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

4s such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pyidyl or pyidylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C₁-C₄)alklyl; C₅-aryl; substituted C₅-aryl (substitution selected from halo,(C₁-C₄)alkoxy, trihalo(C₁-C₃)alklyl, nitro, amino, cyano, (C₁-C₄)alkoxycarbonyl, (C₁-C₃)alklyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

5 such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O,S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-10 piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; hydroxy group, mercapto group; mono- or distraight or branched (C1-C6)alkylamino group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl or 1-methyl-1-ethylpropyl amino; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such as bromomethyl, 15 fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2difluoroethyl, 2,2,2-trifluoroethyl, 2-chloroethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl, 2-bromoethyl or 2iodoethyl; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, trifluoroacetyl, (C3-C6)cycloalkylcarbonyl, (C<sub>6</sub>-C<sub>10</sub>)aroyl selected from benzoyl or naphthoyl, halo substituted (C<sub>6</sub>-C<sub>10</sub>)aroyl such as pentafluorobenzoyl, 4-chlorobenzoyl, 3-bromobenzoyl or 3,4-difluorobenzoyl, (C1-C4)alkylbenzoyl such 20 as 4-toluoyl, 2-toluoyl or 4-(1-methylethyl)benzoyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se

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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrollidnyl, 3-pyrrollidnyl, 2-pyrrollinyl, tetrahyl-tortanyl, turanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ , Q, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-lmidazol,4:5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₄-aryl; substituted C₄-aryl (substitution selected from halo,(C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)alkoxycarboryl, (C₁-C₃)alkylamino or carboxyl; (C₁-C₃)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

s such as 7-butyrolactam, 7-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>2</sub>)alkythiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-embtyl-2-3-dioxo-1-piperazinyl, 4-embtyl-2-3-dioxo-1-piperazinyl, 4-embtyl-2-3-dioxo-1-piperazinyl, 4-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched betwoycarbonyl.

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alklyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>2</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>7</sub>-C<sub>2</sub>)aralklyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto.

Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, Indolyl, 2-pyrrolidinyl, 3-pyrolidinyl, 2-pyrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofthienyl, thienyl, benzofthienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ . O. S or Se

40 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-bjpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heleroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>9</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl

such as y-butyrolactam, y-butyrolactane, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>2</sub>) alkythiopyridazinyl, or a six membered saturated ring with

one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-piperazinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 3-dioxomorpholinyl, 3-di

Z = N, O, S or Se

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20 such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofurianyl, thornyl, benzofuranyl oselonazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or gyridor ing fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, so S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halb,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbornyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxy); (C<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-so propyl

such as  $\gamma$ -butyrolactam,  $\gamma$ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heleroatoms such as pyridyl, pyridazinyl, pyriadinyl, pyrimidinyl or (Cr-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heleroatoms and an adjacent appended O heleroatom such as 2,3-dioxo-1-piperazinyl, 4-entyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxon-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or -(CH<sub>2</sub>),CODR<sup>2</sup> where n = 0-4 and R<sup>2</sup> is selected from hydrogen; straight or branched (Cr-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (Cc-C<sub>1</sub>-1)alkyl selected from phyly selected from phenyl, e-nabhyl or 8-mashhyl or 8-mashhyl is with the proviso that R<sup>2</sup> and R<sup>2</sup> cannot both

hydrogen;

or R<sup>5</sup> and R<sup>5</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>6</sub> and n=0-1, -NH, -N-(Cr-C<sub>3</sub>)alkcyl [straight or branched], -N(C<sub>1</sub>-C<sub>3</sub>)alkcyv, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or motal comploxes.

Preferred compounds are compounds according to the above formula I and II in which X is selected from amino, NRI'R<sup>2</sup>, or halogen; the halogen is selected from bromine, chlorine, fluorine or iodine; and when X = NRI'R<sup>2</sup> and R<sup>2</sup> = hydrosen,

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R<sup>1</sup> = methyl or ethyl,

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R<sup>4</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>6</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected 15 from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C1-C3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C3-C6)cycloalkylgroup selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C1-C3)alkyl, cyano, amino or (C1-C3)acyl); (C6-C10)aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -20 naphthyl; substituted (C6-C10)aryl group (substitution selected from halo,(C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); α-amino(C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from aminomethyl, α-aminoethyl, α-aminopropyl or α-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, a-aminobutyric acid or a-aminopropionic acid and their optical isomers; (C2-C3)aralkylamino group such as phenylglycyl; (C1-C4)alkoxycarbonylamino substituted (C1-C4)alkyl 25 group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy-1-methylethyl or α-hydroxypropyl; halo(C1-C3)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl or 2-iodoethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a 30 benzo or pyrido ring fused thereto:

(A) ., (3)

Z = N, O, S or Se

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such as pyrrollyl. N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofuranyl, titienyl, benzofuranyl, or a five membered aromatic ring with two N. O. S or Se heteroatoms optionally having a benzo or pyrido ring fused thereity.

Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pytdyl or pytdylimidazolyl, or a five membered saturated ring with one or two N, O. S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alky); C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>9</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as y-butyrolactam, y-butyrolactono, imidazolidinone or N-aminoimidazolidinone, or a six membered for aromatic ring with one to three N. O. S. or Se heteroatoms such as pyridyr, pyridazinyl, symthone or two N. O. S. or Se heteroatoms such as pyridyr, pyridazinyl, symthone or two N. O. S. or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-ethyty-2-dioxo-1-piperazinyl, 4-ethyty-2-dioxo-1-piperazinyl, 4-ethyto-2-dioxo-1-piperazinyl, 4-ethyto-2-dioxo-1-piperazinyl,

Z = N. O. S or Se

such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, 40 furanyl, benzofuranyl, tetrahydrofhienyl, thienyl, benzofhienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heterocatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heterotatoms and an adjacent appended O heteroatom.

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(A is selected from hydrogen; straight or branched (C1-C4)alkyl; C5-aryl; substituted C6-aryl (substitution selected from halo,(C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C3)aralkyl group selected from benzy), 1-phenylethyl, 2-phenylethyl or phenylpropyl)

15 such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-20 piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbony) or allyloxycarbonyl; vinyl or substituted vinyl group [substitution selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl group, halogen, (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl, β-naphthyl, substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)-25 alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy), halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2-difluoroethyl, 2,2,2-trifluorcethyl, 2-bromoethyl or 2-iodoethyl, a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se

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40 such as pyrroly), N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyll: (C1-C4)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy,n-butoxy or tert-butoxy; C6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); (C<sub>7</sub>-C<sub>10</sub>)aralkyloxy group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; 45 vinyloxy or substituted vinyloxy group (substitution selected from (C<sub>1</sub>-C<sub>4</sub>)alkyl, cyano, carboxy, or (C<sub>6</sub>-C<sub>10</sub>)aryl selected from phenyl, α-naphthyl or β-naphthyl); RaRbamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; or 50 RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, npropyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R®Rb is (CH2)n, n = 2-6, or -(CH2)2W-(CH2)2- wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; and when  $R = R^4(CH_2)_nCO$ - and n = 1-4,

55 R4 is selected from hydrogen; (C1-C3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; amino; monosubstituted amino selected from straight or branched (Ct-C6)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1pyrrolyl. 1-(1,2.3-triazolyl) or 4-(1,2.4-triazolyl); (C<sub>2</sub>-C<sub>0</sub>-layl) group selected from phenyl, a-naphthyl or β-naphthyl, substituted (C<sub>4</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkyn, trihaelo(C<sub>1</sub>-C<sub>2</sub>)alky, nitro, amino, cyano, (C<sub>1</sub>-C<sub>1</sub>)alkynyl group, (C<sub>1</sub>-C<sub>2</sub>)alkylamino or carboxyl; acyloxy or haloacyloxy group, selected from acstyl, propionyl, chloroacetyl, (tc<sub>1</sub>-C<sub>2</sub>)aryl superior menzoyl or naphthylo, halo substituted (C<sub>2</sub>-C<sub>1</sub>)aryl superior partiallucrobenzoyl, 4-(horoacetyn), 3-bromobenzoyl or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one No. S or Se heterotam opionally having a benzo or pyridor fing legal therefore.

Z = N, O, S or Se

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such as pyrrollyi. N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollnyl, tetrahydroturanyl, of furanyl, benzofuranyl, tetrahydrottrienyl, thinnyl, benzofurenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazolyl-5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteratoms and an adiacent aponeded O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, hitho, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoy,carbonyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxy); (C<sub>7</sub>-C<sub>6</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

so such as 7-butyrolactam, 7-butyrolactone, imidazoldinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. Q. S. or Se heterostoms such as pyridy, pyridaziny, pyraziny, symptriaziny, unsym-triaziny, unsym-triaziny, pyrimdinyl or (C;-C;)alkylthiopyridazinyl, or a six membered saturated ring with one or two N. Q. S or Se heterostoms and an adjacent appended O heterostom such as 2;5-dioxo-1-piperazinyl, 4-edipyrezy-dioxo-1-piperazinyl, 4-edipyrezy-dioxo-1-pip

[straight or branched]. NNI. NOB [B is selected from hydrogen or (G,-C<sub>2</sub>)alkyl], O or S; or R\*R\*aminoxy group, wherein R\*R\*B is a straight or branched (G,-C<sub>2</sub>)alkyl selected from methyl, othly, n-propyl, 1-methyletyl, n-buyl, 1-methyletyl, 1-meth

## Z = N. O. S or Se

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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, 25 furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromaticring with two N, O, S or Se heteroatoms obtionally having a benzo or pyrdod ring fused thereto:

## $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imizor(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom:

50 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxy); (C<sub>7</sub>-C<sub>4</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-pronyll

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered s aromatic ring with one to three N, O.S or Se heterosations such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (Cr-C<sub>3</sub>)alkythtiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-entlyt-2,3-dioxo-1-piperazinyl, 4-entlyt-2,3-dioxo-1-piperazinyl, 4-entlyt-2,3-dioxo-1-piperazinyl, 4-oreptity-2,3-dioxo-1-piperazinyl, 4-oreptity-2-dioxo-1-piperazinyl, 4-oreptity-2-di piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; hydroxy group; a-hydroxy(Ci-C<sub>2</sub>)alkyl group selected from hydroxymethyl, e-hydroxyethyl or a-hydroxy-i-methylethyl or a-hydroxyropyl; halo(Ci-C<sub>2</sub>)-alkyl group such as bromomethyl, fluoromethyl, eliuromethyl, chioromethyl, chioromethyl,

Z = N. O. S or Se

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20 such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^{\dagger} = N \Omega S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (G.-Ca,)alkyl; C-c\_anyl; substituted Cs\_anyl (substitution selected from halo,(G-0,3 alkovy, trihat(O-0,3 alkyl, niro, cyano, (C,-C-0) alkovy,catoponyl, (G-0,5) so alkylamino or carboxy); (G;-Ca)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-provint

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. 5 or Se heteroatoms such as pyridy, pyridaziyl, pyraziyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>2</sub>)-alkythiopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-edityl-2-dioxo-1-piperazinyl, 4-edityl-2-dioxo-1-pipe

ycarbonylamino;

and when  $R = R^4$  (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>- and n = 0,

R<sup>o</sup> is selected from amino; monosubstituted amino selected from as straight or branched (c,--c<sub>s</sub>)alloylamino, cyclopropylamino, beoxylamino e prohylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(t-methylathyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1/2-3-tirazoly) or 4-(1/2-4-tirazolyl); straight or branched (G,--C<sub>s</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyli, (C,-C<sub>s</sub>)alkyl group selected from phenyl, αnapithyl or β-napithyl; substituted (C<sub>s</sub>--C<sub>s</sub>)alkoy, group (c,--C<sub>s</sub>)alkylamino or carboxyl; a heterocycle tribalo(C,--C<sub>s</sub>)alkyl, nitro, amino, cyano, (C,--C<sub>s</sub>)alkoy, (C,--C<sub>s</sub>)alkylamino or carboxyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ing flusted thereto:

7 = N. O. S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothlenyl, thienyl, benzothlenyl or selenazolyl,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-midazolyl-5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N. O. S or Se heteroatoms and an adiacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

ss such as ¬-butyrolactam, ¬-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsymtriazinyl, pyramindinyl or (Ci-C<sub>2</sub>)alk/ythiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxort-

piperazinyl, 4-athyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxonorpholinyl or 2-dioxothiomorpholinyl; and when  $R = \mathbb{R}^q$  (Clt<sub>2</sub>), $\mathbb{S}Q_2$ - and n = 1-4,

R<sup>4</sup> is selected from hydrogen; antino; monosubstituted amino selected from straight or branched (G--C<sub>2</sub>)-alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, disthylamino, monomethylbenzylamino, piperidinyl, monopholinyl, 1-imidazolyl, 1-pyrrolyl, 1-t1(2,3-triazolyl) or 4-t1(2,4-triazolyl); straight or branched (G--C<sub>2</sub>)alkyl group selected from methyl, ethly, n-propyl or 1-methylethyl, (G--C<sub>1</sub>)alkyl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (G--C<sub>1</sub>)alkoy group (C1-C<sub>2</sub>)alkylmino selected from halo, (G--C<sub>2</sub>)alkoy, trihalo(C1-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C1-C<sub>2</sub>)alkoyzerbonyl, (C1-C<sub>2</sub>)alkylmino or carboxyl; (C1-C<sub>1</sub>)alkoy, group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy, iso-butoxy or tert-butoxy; C6-aryloxy group

selected from phenoxy or substituted phenoxy (substitution selected from halo, (C,-C<sub>4</sub>)sikyl, nitro cyano, thiol, amino, carboxy, difc-C<sub>9</sub>)sikylamiro, (C,-C<sub>9</sub>)sikylamiro, (C,-C<sub>9</sub>)sikylamiro, selected from such as benzyloxy, 1-phenylethyloxy; or 2-phenylethyloxy; (C,-C<sub>9</sub>)carboxyalkyl group; 18 Seelected from hydrogen; straight or branched (C,-C<sub>9</sub>)sikyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>9</sub>-C<sub>9</sub>)sralkyl group selected from phenyl, a-naphthyl or β-naphthyl; (C<sub>9</sub>-C<sub>9</sub>)sralkyl group

or 1-methylethyl;  $(C_s \cdot C_{10})$ aryl group selected from phenyl, a-naphthyl or  $\beta$ -naphthyl;  $(C_s \cdot C_s)$ aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

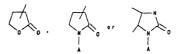
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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofurinyl, titienyl, benzofurinyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyriod ring fused thereto:

Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3allyl-SH-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a live membered saturated ring with one or two N, O, 45 S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (G,-C<sub>4</sub>)alky): C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(G<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(G<sub>1</sub>-C<sub>5</sub>)alky), nitro, amino, cyano, (G<sub>1</sub>-C<sub>4</sub>)alkoycarbony), (G<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (G<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl and the selected from benzyl (G<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl (G<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl 2-phenylethyl or phenylethyl (G<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl 2-phenylethyl or phenylethyl (G<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl 2-phenylethyl (G,-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl 2-phenylethyl 1-phenylethyl 1-phe

propyl)

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such as y-bulyrolactam, y-bulyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-miazinyl, pyrimdinyl or (G-C-3)alkylthlopyridazinyl, or a six membered saturated ring with s one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,2-dioxo-1-piperazinyl, 4-ethyl-2,2-dioxo-1-piperazinyl, 2-dioxom-pholinyl; or -(CH<sub>2</sub>),COOR? where n = 0-4 and R? is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl, or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methylethyl or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl ethyl or t-methylethyl or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methyl ethyl or t-methylethyl or (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or t-methyl ethyl or t-methyl ethyl ethy

10 R<sup>6</sup> is selected from hydrogen; straight or branched (Ch-C<sub>2</sub>)alklyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>2</sub>-C<sub>2</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>2</sub>-C<sub>3</sub>)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fixed therefor.

Z = N. O. S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrathydrofuranyl, turanyl, benzothranyl, tetrathydrofuranyl, benzothranyl, tetrathydrofuranyl, benzothranyl, tetrathydrofuranyl, benzothranyl, tetrathydrofuranyl, tetrathydrofuranyl, benzothranyl, tetrathydrofuranyl, tetrathydrofuran

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

ss such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-midazolyl, 45-bjpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatoms:

(A is selected from hydrogen; straight or branched (C₁-C₂)alkyl; C₂-aryl; substituted C₂-aryl (substitution so selected from halo,(C₁-C₂)alkoy, trihalo(C₁-C₂)alkyl, nitro, amino, cyano, (C₁-C₂)alkoxycarbonyl, (C₁-C₂)alkylamino or carboxy); (C₂-C₂)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyll

such as y-bulyrolactam, y-bulyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (Cy-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, armship-1/2,3-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxomorpholi

from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C<sub>6</sub>-C<sub>10</sub>)aryl selected from phenyl, -naphthyl or Hanphithyl; with the proviso that R³ and R³ cannot both be hydrogen; or R³ and R³ caken together are -(CH<sub>2</sub>)-W(CH<sub>2</sub>)-, wherein W is selected from (CH<sub>2</sub>), and n=0-1, -NH, -N(C<sub>1</sub>-C<sub>2</sub>)alkyl [straight or branched]. N(C<sub>1</sub>-C<sub>4</sub>)alkoxy, oxygen, sulfur or substituted congeners s selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and innovanic salts or metal complexes.

Particularly preferred compounds are compounds according to the above formula I and II in which X is selected from amino, NRPR, or hadgen; the hadgen is selected from bromine, chlorine, fluorine or iodine; and when X = NRPR and R<sup>1</sup> = invdrogen.

10 R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R<sup>1</sup> = methyl or ethyl.

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

R is selected from  $R^{\epsilon}(CH_2)_nCO$ - or  $R^{\epsilon'}(CH_2)_nSO_2$ -; and when  $R=R^{\epsilon}(CH_2)_nCO$ - and n=0,

R4 is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C1-C5)-15 alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C1-C3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C3-C6)cycloalkylgroup selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C5)cycloalkyl group (substitution selected 20 from (C<sub>1</sub>-C<sub>3</sub>)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or βnaphthyl; substituted (C<sub>5</sub>-C<sub>10</sub>)aryl group (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); α-amino-(C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from aminomethyl, α-aminopthyl, α-aminopropyl or α-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, α-aminobutyric acid or α-aminopropionic acid and their optical isomers; 25 (C<sub>7</sub>-C<sub>9</sub>)aralkylamino group such as phenylglycyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino substituted (C<sub>1</sub>-C<sub>4</sub>)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; a-hydroxy(C1-C3)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy-1-methylethyl or α-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl or 2-iodoethyl; a heterocycle group selected 30 from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, Indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofthienyl, thienyl, benzofthienyl or selenazotyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N. O. S$  or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3s alkyl-3H-imidazol4,5-b]pyridyl or pyridyllimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C;-C<sub>2</sub>)alkyl; C<sub>4</sub>-aryl; substituted C<sub>4</sub>-aryl (substitution selected from halo,(G;-C<sub>4</sub>)alkoxy, trihalo(C;-C<sub>3</sub>)alkyl, nitro, amino, cyano, (G;-C<sub>4</sub>)alkoxycarbonyl, (G;-C<sub>5</sub>)arklylamino or carboxy); (G;-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

15 such as --butyrolactam, --butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatons such as pyridyl, pyrtdazinyl, pyrtazinyl, activity-23-dioxo-1-piperazinyl, 4-entiply-23-dioxo-1-piperazinyl, 4-entiply-23-dioxo-1-piperazi

#### Z = N, O, S or Se

such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolidnyl, 3-pyrrolidnyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofurianyl, benzofurianyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or ovyido ning fused thereto:

# Z or $Z^1 = N$ , O, S or Se

so such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

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- 10 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarboryl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylathyl or phenylpropyl)
- such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridy), pyridazinyl, ysymtiazinyl, unsym-triazinyl, pyrimidinyl or (Cr-C<sub>2</sub>)alky(thtopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 4-emthyl-2-3-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (Cr-C<sub>2</sub>)alkoyucarbonyl group selected from 2-dioxothiomorpholinyl, 3-anaphthyl, 3-shaphthyl, substituted (C<sub>2</sub>-C<sub>2</sub>)akyl group, halogen, (C<sub>2</sub>-C<sub>3</sub>-)aryl group substitution selected from halo, (Cr-(2)alkyov, trihalo(Cr-C<sub>3</sub>)alkyl nitro, amino, cyano, (Cr-C<sub>2</sub>-) alkoyucarbonyl, (Cr-C<sub>3</sub>-alkylamino or carboxyl, halo(Cr-C<sub>3</sub>-C<sub>3</sub>-)alkyl group such as bromomethyl, flucromethyl, 2-dioxomethyl, 3-dioxomethyl, 3-d

Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzofhienyl or selenazolyl];

- 40 (G-C-)alkoxy group such as allyloxy, methoxy, ethoxy, re-propoxyn-butoxy or ten-butoxy; C<sub>2</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (G-C<sub>2</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, diG-C<sub>2</sub>)alkylamino(j, G-C<sub>2</sub>-a)arylamino(j, G-C<sub>2</sub>-a)arylamino(j, C-C<sub>2</sub>-a)arylamino(j, C-C<sub>2</sub>-a)arylamino
- methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R\*R\* is (CH<sub>2</sub>), n=2-6, or -(CH<sub>2</sub>):W(CH<sub>2</sub>): wherein W is selected from -N(C<sub>1</sub>-C<sub>2</sub>)alkyl (straight or branched), -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>2</sub>)alkyl), O or S;

and when R = R4 (CH2), CO- and n = 1-4,

R¹ is selected from hydrogen; (C₁-C₂)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; amino, monosubstituted amino selected from straight or branched (G₁-C₂)alkylamino, cyclopropylamino, cyclobuylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-limidazolyl, 1-pyrrolyl, 1-1(1,2-litazolyl) or 4-(1,2-triazolyl); (C₄-C₁₀)aryl group selected from phanyl, a-naphthyl or β-naphthyl; substituted (Q₄-C₁₀) aryl group (substitution selected from halo, (G₁-C₄)alkovy, thinalo(G₁-C₃)alkyl.

nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); acyloxy or haloacyloxy group, selected from acetyl, propionyl, chloroacetyl, trichloroacetyl, (C<sub>3</sub>-C<sub>5</sub>)cycloalkyloarbonyl, (C<sub>3</sub>-C<sub>1</sub>-C<sub>3</sub>)anyl) such as epentafluorobenacyl, 4-chlorobenacyl, 3-bromobenacyl or 3,4-difluorobenacyl, (C<sub>1</sub>-C<sub>4</sub>)alkylbenacyl such as 4-toluoyl, 2-toluoyl, 4-(1-5 methylethylbenacyl) or (heterocyclojarbonyl, the heterocycle selected from a five membered aromatic or saturated rino with one Who and a such accordance or cyridor in clusted thereto:

# Z = N, O, S or Se

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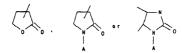
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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furranyl, benzofuranyl, tetrahydrothienyl, thienyl, benzofthienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

# $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b[pyridyl or pridyl/limidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appeneded 0 heteroatom:



- 40 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, arnino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>2</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
- such as 7-butyrolactam, 7-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. Q. S. or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtone or two N. Q. S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxor1-piperazinyl, 4-embtyl-2-3-dioxor1-piperazinyl, 4-embtyl-2-piperazinyl, 4-embtyl-2-piperazinyl, 4-embtyl-2-piperazinyl, 4-embtyl-2-piperazinyl, 4-embtyl-2-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl, 4-embtyl-2-pipyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1-piperazinyl-2-dioxor1

group selected from methythitio, ethythio, propylthio or allythio; C<sub>2</sub>-arythio group selected from phenylthio resubstituted phenylthio (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>2</sub>) alkylamino); C<sub>2</sub>-arythiol group selected from phenylsultonyl or substituted phenylsultonyl group selected from phenylsultonyl nitro, amino, cyano, (C<sub>1</sub>-C<sub>3</sub>)-alkoxy, trihalc(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>3</sub>)-alkoxy, trihalc(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>3</sub>)-alkoxy, and the consequence of th

#### Z = N. O. S or Se

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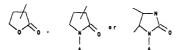
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20 such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, letrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofthienyl, thienyl, benzofthienyl or selenazolyl, or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto.

#### $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-limidazo4,5-bjpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N. O, 35 S or Se heteroatoms and an adjacent appended O heteroatom:



- (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxyl; (C<sub>2</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl
- 50 such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O.3 or Se heterostoms such as pyridyl, pyridazinyl, pyrazinyl, symptriazinyl, unsym-triazinyl, pyriamidyl (C<sub>1</sub>-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O. So of Se heterostoms and an adjacent appended O heterostom such as 2,3-disco-1-piperazinyl, 4-etyclopy-2-disco-1-piperazinyl, 2-disco-5-disco-1-piperazinyl, 2-disco-6-disco-1-piperazinyl, 2-disco-6-disco-1-piperazinyl, 2-disco-6-disco-1-piperazinyl, 2-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disco-6-disc

selected from acetyl, propionyl, chloroacetyl, trifluoroacetyl, (C<sub>2</sub>-C<sub>2</sub>-bycloalky/carbonyl, (C<sub>2</sub>-C<sub>1</sub>-c) aroyl selected from benzcyl or naphthoyl, halo substituted (C<sub>2</sub>-C<sub>1</sub>-b) aroyl such as pentafluorobenzoyl, 4-chlorobenzoyl, C<sub>1</sub>-c<sub>1</sub>-b) such as from 4-folionyl, 2-folionyl or 4-(1-methylethyl)benzoyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with non N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

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15 such as pyrrolyi, N-methylindolyi, indolyi, 2-pyrrolidinyi, 3-pyrrolidinyi, 2-pyrrolinyi, tetrahydrofuranyi, turanyi, benzofuranyi, tetrahydrothienyi, titerahy, benzothienyi or selenazolyi, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, lthiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, Sor Se heteroatoms and an adiacent apoended O heteroatom:

40 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>4</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as --butyrolactam, --butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G<sub>2</sub>)alkylthlopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-drepty-2-d-dioxo-1-piperazinyl, 4-drepty-2-d-dioxo-1-piperazinyl, 4-drepty-2-d-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl: (Ci-C<sub>4</sub>)alkoxycarbonylamino group selected from se tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino.

and when  $R = R^4(CH_2)_nSO_2$ - and n = 0,

R<sup>4</sup> is selected from amino: monosubstituted amino selected from as straight or branched (C<sub>1</sub>-C<sub>2</sub>)-alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylibenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (G<sub>2</sub>-C<sub>1</sub>)aryl group selected from phenyl, anaphthyl or β-naphthyl; substituted (G<sub>2</sub>-C<sub>1</sub>)alayl group ubstitution selected from halo, (G<sub>2</sub>-C<sub>1</sub>)alayl group selected from phenyl, anaphthyl or β-naphthyl; substituted (G<sub>2</sub>-C<sub>1</sub>)alayl group (substitution selected from halo, (G<sub>2</sub>-C<sub>1</sub>)alayl).

trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoycarbonyl, (C<sub>1</sub>-C<sub>2</sub>)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

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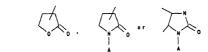
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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzothranyl, tetrahydrofuranyl, benzothranyl, tetrahydrofuranyl, benzothranyl, tetrahydrofuranyl, turanyl, benzothranyl, tetrahydrofuranyl, t

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-rayl; substituted C<sub>6</sub>-rayl (substitution selected from halo;(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo;(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>) alkylamino or carboxyl; (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. Q. S or Se heteroatoms such as pyridy, pyridaziny, pyramiyl, symtrazinyl, unsym-triazinyl, pyrimidinyl or (Ci-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with 45 one or two N. Q. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-ettlyk-2,3-dioxo-1-piperazinyl, 4-ettlyk-2,3-dioxo-1-piperazinyl, 4-ettlyk-2,3-dioxo-1-piperazinyl, 4-dioxomorpholinyl or 2-dioxontiomorpholinyl; and who R = Rf (Crt-L<sub>2</sub>)C<sub>2</sub> and n = 1.4.

and minin — "A (1973),852° and 11-15-15.

R\* is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (Ci-Cs)so alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, dishtylamino, ethyl-methylamino, ethyl-methyl

 $(CH_2)_2$ - wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S;

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>2</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, -p-propyl or 1-methylethyl; (C<sub>4</sub>-C<sub>1</sub>)aryl group selected from phenyl, a-naphthyl or β-naphthyl; (C<sub>7</sub>-C<sub>2</sub>)aralkyl group s such as benzyl. 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or gvirdo ring fused thereto:

Z = N. O. S or Se

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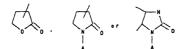
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such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolldinyl, 2-pyrrolldinyl, 2-pyrrollnyl, tetrahydroduranyl, turanyl, benzofuranyl, tetrahydrothlenyl, thienyl, benzothlenyl or selenazolyl, or a five membered aromatic 20 ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ , Q, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxyl; (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl

such as  $\gamma$ -butyrolactam,  $\gamma$ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, sym-triazinyl, pyrimidinyl or (Cl-C<sub>2</sub>)alky/thiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-entryl-2.3-dioxo-1-piperazinyl, 4-entryl-2.3-

Rf is selected from hydrogen; straight or branched (G-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (G-C<sub>2</sub>-C<sub>2</sub>)arkyl group selected from phenyl, e-naphthyl or  $\beta$ -naphthyl; (G-C<sub>2</sub>-C<sub>3</sub>)arakyl group such as benzyl, 1-přenylethyl, 2-přenylethyl or phenylpropyl; a heterocycle group selected from a five

membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



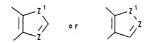
Z = N, O, S or Se

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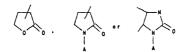
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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, letrahydroturanyl, furranyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, ithlazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-bjpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended 0 heteroatom:



40 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as \_-bulyrolactam, \_-bulyrolactone, imidazoidinone or N-aminoimidazoidinone, or a six membered aromatic ring with one to three N. O., S or Se heteroatoms such as pyridyl, pyridazinyl, symtiazinyl, unsym-triazinyl, pyrimdinyl or (Cr-Cs\_)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-entryl-2,3-dioxo-1-piperazinyl, 4-entryl-2,3-dioxo-1-piperazinyl, 4-entryl-2,3-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl, or (CH<sub>2</sub>),COOR<sup>2</sup> where n = 0-4 and R<sup>2</sup> is selected from mydrogen; straight or branched (Cr-Cs\_)alkyl selected from methyl, ehyl, n-propyl or 1-methylethyl; or (C<sub>2</sub>-C<sub>2</sub>) and selected from the control of the R<sup>2</sup> and the control of the control

R<sup>2</sup> cannot both be hydrogen; or R<sup>2</sup> and R<sup>2</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>-W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n = 0-1, -NH, -N-(C<sub>1</sub>-C<sub>2</sub>)alky [straight or branched], -N(C<sub>1</sub>-C<sub>4</sub>)alkoxy, oxygen, sulfur or substituted congeners selected from 50 (L or Djoroline, ethyl(L or Djoroline), enhyl(L or Djoroline), ethyl(L or D

Most particularly preferred compounds are compounds according to the above formula I and II in which X is selected from amino, NR1R2, or halogen;

the halogen is selected from bromine, chlorine, fluorine or iodine; and when  $X = NR^1R^2$  and  $R^1 = hydrogen$ .

 $R^2 = \text{methyl}$ , ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when  $R^1 = \text{methyl}$  or ethyl,

s  $R^2$  = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; R is selected from  $R^4(CH_2)_nCO$ - or  $R^4'(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R<sup>+</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkylamino, cyclophyshamino, cyclophyshamino, benzylamino or phenylamino, disbuthuted amino selected from dimethylamino, diethylamino, ethyl(f-methylathyl)amino, monomethylbenzylamino, piperdimyl, morpholinyl, 1-midazoyl, 1-yorrollyl, 1-f(2-3/alazoyl) or 4-f(1-2-4-tiazoyl); straight or branched (G-C<sub>2</sub>-D<sub>2</sub>)lyly group selected from methyl or ethyl; (C<sub>4</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>4</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (G--C<sub>3</sub>)alkoxy, trihalo(G--C<sub>3</sub>)alkyl, nitro, amino, yoan, (G--C<sub>3</sub>)alkyl group selected from halo α-mainopropionic acid and their optical isomers; αlydroxy(G-C<sub>3</sub>)alkyl group selected from hydroxymethy, α-hydroxyyethy α-hydroxyethy, α-hydroxyyethy, α-hydroxyethy, α-hydroxyethy, chloromethyl, dichloromethyl, tichloromethyl, 2-Guloroethyl, 2-gu

Z = N. O. S or Se

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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, 30 furanyl, benzofuranyl, tetrahydroftilenyl, thienyl, benzothlenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se beteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C₁-C₂)alkyl; C₂-aryl; substituted C₂-aryl (substitution selected from halo,(C₁-C₂)alkoy, trihalo(C₁-C₂)alkyl, nitro, amino, cyano, (C₁-C₂)alkoxycarbonyl, (C₁-C₂)-salkylamino or carboxy); (C₂-C₂)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as  $\gamma$ -butyrolactam,  $\gamma$ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-

triazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>3</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl group selected from 5 methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl; vinyl or substituted vinyl group [substitution selected from (C1-C3)alkyl group, halogen,  $(C_6-C_{10})$ aryl group selected from phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, substituted  $(C_6-C_{10})$ aryl group alkoxycarbonyl, (C1-C3)alkylamino or carboxy), halo(C1-C3)alkyl group such as bromomethyl, fluoromethyl, 10 difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl or 2-iodoethyl, a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused



Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl]; (C1-C4)alkoxy group such as 25 allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or tert-butoxy; C<sub>6</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo,  $(C_1-C_4)$ alkyl, nitro, cyano, thiol, amino, carboxy,  $di(C_1-C_4)$ alkyl, nitro, cyano, thiol, amino, cyano, cyano C<sub>3</sub>)alkylamino); (C<sub>7</sub>-C<sub>10</sub>)aralkyloxy group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; vinyloxy or substituted vinyloxy group (substitution selected from (C1-C4)alkyl, cyano, carboxy, or (C6-C10)aryl selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl);  $R^aR^b$ amino( $C_1$ - $C_4$ )alkoxy group, wherein  $R^aR^b$  is a 30 straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n=2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_2)_2W(CH_2)_2$ - where  $-N(C_1-C_2)_2W(CH_2)_2W(CH_2)_2$ - where  $-N(C_1-C_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2W(CH_2)_2$ C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; or ReReaminoxy group, wherein ReRe is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, npropyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n=2-6, or  $-(CH_2)_2W^{-1}$ 35 (CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>0</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyi], O or S;

and when  $R = R^4(CH_2)_nCO$ - and n = 1-4,

R<sup>4</sup> is selected from hydrogen; (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl; amino; monosubstituted amino selected from straight or branched (C1-C6)alkylamino, cyclopropylamino, cyclobutylamino, ben-40 zylamino or phenylamino, disubstituted amino selected from dimethylamino, diethylamino, ethyl(1methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3triazolyl) or 4-(1,2,4-triazolyl); ( $C_6$ - $C_{10}$ )aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl;  $substituted(C_6-C_{1\,0}) aryl\ group\ (substitution\ selected\ from\ halo,\ (C_1-C_4) alkoxy,\ trihalo(C_1-C_3) alkyl,\ nitro,$ amino, cyano, (C1-C4) alkoxycarbonyl, (C1-C3) alkylamino or carboxy); acyloxy or haloacyloxy group, se-45 lected from acetyl, propionyl, chloroacetyl, trichloroacetyl, (C3-C6)cycloalkylcarbonyl, (C6-C10)aroyl selected from benzoyl or naphthoyl, halo substituted (C6-C10) aroyl such as pentafluorobenzoyl, 4-chlorobenzoyl, 3bromobenzoyl or 3,4-difluorobenzoyl, (C1-C4)alkylbenzoyl such as 4-toluoyl, 2-toluoyl, 4-(1-methylethyl)benzoyl or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated nng with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



## Z ≈ N, O, S or Se

such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrollidinyl, 3-pyrrollidinyl, 2-pyrrollidinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazoly), or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

### Z or $Z^1 = N, O, S$ or Se

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3s alky-3H-Imidazol(4,5-b]pyridy| or pyridy|imidazolyl, or a five membred saturated ring with one or two N. O, S or So heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C;-C<sub>c</sub>)alkyl; C<sub>c</sub>-aryl; substituted C<sub>c</sub>-aryl (substitution selected from halo,(G;-C<sub>c</sub>)alkoxy, trihalo(C;-C<sub>c</sub>)alkyl, nitro, amino, cyano, (C;-C<sub>c</sub>)alkoxycarbonyl, (C;-C<sub>c</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

30 such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one or two N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>3</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-35 piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or tert-butoxy; RaPamino(C1-C4)alkoxy group, wherein RaPa is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2methylpropyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2 W(CH2)2- wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or RaRbaminoxy 40 group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2W(CH2)2wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl<sub>1</sub>,O or S: α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or αhydroxy-1-methylethyl or α-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoromethyl, 2-bromoethyl or 2-iodoethyl; (C1-C4)alkoxycarbonylamino group selected from tertbutoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino;

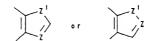
# and when $R = R^4(CH_2)_nSO_2$ - and n = 0,

50 Pt is selected from amino; monosubstituted amino selected from as straight or branched (c,-c<sub>k</sub>)-allyslamino, cyclopropyslamino, percybartino or phanylamino; dissubstituted amino selected from dimethylamino, diethylamino, ethyl(t-methylethyl)amino, monomethylbonzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-t(1,2-driazoly)) or 4-t(1,2-4-trazolyl); straight or branched (C,-c<sub>k</sub>-)alkyl group selected from methyl or ethyl; (c<sub>k</sub>-c<sub>k</sub>-)alkyl group selected from penhyl, «naphthyl or £naphthyl) or £naphthyl; se substituted (c<sub>k</sub>-c<sub>k</sub>-)aryl group (substitution selected from halo, (C,-c<sub>k</sub>-)alkoxy, thialo(C,-c<sub>k</sub>-)alkyl, nitro, amino, cyano, (C<sub>k</sub>-c<sub>k</sub>-)alkoxycarboxyl, (C,-c<sub>k</sub>-)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se

10 such as pyrroli/i, N-methylindolyl, indolyl, 2-pyrrolidnyl, 3-pyrrolidnyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofurienyl, thienyl, bonzofurenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or 8-beteroatoms optionally having a benzo or pyrido ring fused thereto:

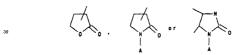


 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

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such as Imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



- 36 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>3</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (G-C<sub>3</sub>)alkoxycarbonyl, (G<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxyl; (G<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
- such as -y-butyrolactam, -y-butyrolactone, imidazoldinone or N-aminoimidazoldinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G-)alky/thiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl
- 48 and when R = R\*(CHb<sub>2</sub>)sQ<sub>2</sub>- and n = 1-4, R\* is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl; R\* is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1methylethyl; (C<sub>2</sub>-C<sub>2</sub>-layly) group selected from phenyl, a-naphthyl or \$\text{p-naphthyl}\$; (C<sub>2</sub>-C<sub>2</sub>-laylkyl group such as benzyl, 1-phenylethyl 2-phenylethyl or phenylpropyl, a heterocycle group selected from a five memso bered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



### Z = N. O. S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolidinyl, etrahydrofuranyl, turanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

## $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

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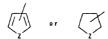
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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazolql.5-bl.pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>4</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as γ-bulyrolactam, γ-bulyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtrazinyl, unsym-trazinyl, pyrimidinyl or (Gr-C<sub>2</sub>)alky/thlopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,2-dioxo-1-piperazinyl, 4-embly-2,2-dioxo-1-piperazinyl, 4-ethyl-2,2-dioxombinomypholinyl; or -(CH<sub>2</sub>)CODR' where n = 0-4 and R' is selected from hydrogen; straight or branched (Gr-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (Cc-C<sub>1</sub>)alvyl group selected from phenyl, α-naphthyl, β-naphthyl, β-f is selected from thyl group selected from phenyl, α-naphthyl; (Gr-C<sub>2</sub>)arkyl group such as benzyl, 1-phenylethyl; 2-phenylethyl or phenyleropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a beancy or pyrido ring lused thereits.



## Z = N. O. S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydroftnienyl, thienyl, benzoftnienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

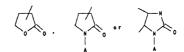
$$\downarrow$$

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-10 alkyl-3H-imidazo(1,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoycarbonyl, (C<sub>1</sub>-C<sub>2</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylze propyl

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. Q. S. or Se heteroatons such as pyridyl, pyridazinyl, pyratiznyl, pyratiznyl, unsym-triazinyl, unsym-triazinyl, pyrimidinyl or (G<sub>1</sub>-C<sub>2</sub>)alky/thiopyridazinyl, or a six membered saturated ring with one or two N. Q. S. or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-23-dioxo-1-piperazinyl, 4

ss or R<sup>5</sup> and R<sup>5</sup> taken together are -{CH<sub>2</sub>}<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>m</sub> and n = 0-1, -NH, -N-(Cr-C<sub>3</sub>)alk(y) [straight or branched], -N(Cr-C<sub>3</sub>)alk(y), oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pytrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Compounds of special interest are compounds according to the above formula I and II in which X is selected from amino, NR, R<sub>2</sub> or halogen; the halogen is selected from bromine, chlorine, fluorine or iodine; and when X = NR\*!R<sup>2</sup> and R\*1 = methyl or ethyl;

R<sup>2</sup> = methyl or ethyl.

R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R<sup>4</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl; a sheterocycle group selected from a five membered aromatic or saturated ring with one N, O, or S heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O or S

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl,

furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, \text{ or } S$ 

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol{3-5b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O or S heteroatoms and an adjacent appended O heteroatom.

(A is selected from hydrogen; straight or branched (C1-C2)alkyl; C6-aryl)

such as -p-butyrolactam, -p-butyrolactone, imidazolidinone for N-aminoimidazolidinone; (G--C<sub>1</sub>)akovycarbonyl, group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched propoxylcarbonyl or allyloxycarbonyl; winyl or substituted vinyl group (substitution selected from (G--C<sub>2</sub>)alkyl group, (G--C<sub>3</sub>)alky) group, (G--C<sub>3</sub>)alky), group such as bromomethyl, fluoromethyl, fluoromethyl, fluoromethyl, difluoromethyl, difluoromethyl, difluoromethyl, fluoromethyl, G-C<sub>3</sub>)alky, (G--C<sub>3</sub>)alky); (G--C<sub>3</sub>)alky), group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or terl-butoxy; G-ayrloxy group selected from phenoxy or substituted phenoxy (substitution selected from hab., (G--C<sub>3</sub>)alky); (G--C<sub>3</sub>)alky); group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; vinyloxy or substituted vinyloxy group (substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butlyl; or R<sup>2</sup>R<sup>2</sup>mininoxy group, subverin R<sup>2</sup>R<sup>2</sup> is a straight or branched (G--C<sub>3</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butlyl; or R<sup>2</sup>R<sup>2</sup>mininoxy group.

and when  $R = R^4(CH_2)_nCO$ - and n = 1-4,

R\* is selected from hydrogen; (C1-C2)alkyl group selected from methyl or ethyl; amino; monosubstituted amino selected from straight or branched (C1-C6)alkylamino, cyclopropylamino, cyclobutylamino, ben-45 zylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, or 1-(1,2,3triazolyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted(C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C1-C4)alkoxy, nitro, amino, (C1-C4)alkoxycarbonyl); acyloxy or haloacyloxy group selected from acetyl, propionyl or chloroacetyl; (C1-C4)alkoxy group such as allyloxy, methoxy, 50 ethoxy, n-propoxy, n-butoxy or tert-butoxy; RaRbamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-55 methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or ReRb is (CH<sub>2</sub>)<sub>n</sub>, n=2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl), O or S; halo(C1-C3)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-

trifluoromethyl, 2-bromoethyl or 2-lodoethyl; (Ci-Ci-)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino;

and when  $R = R^4(CH_2)_nSO_2$  and n = 0,

R<sup>4</sup> is selected from straight or branched (G-C<sub>2</sub>)alkyl group selected from methyl or ethyl; (G<sub>2</sub>-G<sub>1</sub>)aryl group selected from phenyl, a-naphthyl or β-naphthyl; substituted (G<sub>2</sub>-G<sub>10</sub>)aryl group (substitution selected from halo, (G<sub>1</sub>-G<sub>1</sub>)alkoxy, nitro, (G<sub>1</sub>-G<sub>2</sub>)alkoxycarbonyl); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom optionally having a benzo or pyrido ring fused therefor.



Z = N. O or S

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20 such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzothranyl, tetrahydroflinenyl, thionyl, benzothrenyl or selenazolyl, or a five membered aromatic ring with two N, O or S heteroatoms opticnally having a benzo or pyrido ring fused thereto:



 $Z \text{ or } Z^1 = N \text{ } \Omega \text{ or } S$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl,5-b]pyridyl or pyridylimidazolyl;

35 and when  $R \approx R^4 (CH_2)_n SO_2$ - and n = 1-4,

 $\mathbf{R}^d$  is selected from hydrogen; straight or branched ( $\mathbf{G}_1$ - $\mathbf{G}_2$ )alkyl group selected from methyl or ethyl;  $\mathbf{R}^d$  is selected from hydrogen; straight or branched ( $\mathbf{G}_1$ - $\mathbf{G}_2$ )alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R<sup>5</sup> and R<sup>6</sup> cannot both be hydrogen;

or R<sup>5</sup> and R<sup>5</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>-W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n = 0-1, -NH, -N-(G-G<sub>2</sub>)alkyl [straight or branched), -N(G-G<sub>2</sub>)alkovy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrmiolidine or piperidine;and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Also included in the present invention are compounds useful as intermediates for producing the above compounds of formula I and II. Such intermediate compounds include those having the formula:

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25 wherein formula III and IV, Y is NO2;

R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0, R<sup>4</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>6</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, mor-30 pholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (G₁-C₄)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1dimethylethyl; (C3-C6)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C5)cycloalkyl group (substitution selected from (C1-C3)alkyl, cyano, amino or (C1-C3)acyl); (C6-C10)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C6-C10)aryl group (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C9)aralkyl group selected from benzyl, 1-phenylethyl, 2phenylethyl or phenylpropyl; α-amino-(C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from aminomethyl, α-aminoethyl, αaminopropyl or a-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, aaminobutyric acid or α-aminopropionic acid and their optical isomers; (C7-C3)aralkylamino group such as 40 phenylglycyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino substituted (C<sub>1</sub>-C<sub>4</sub>)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or αhydroxy-1-methylethyl or α-hydroxypropyl; α-mercapto(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from mercaptomethyl, αmercaptoethyl, α-mercapto-1-methylethyl or α-mercaptopropyl; halo(C<sub>1</sub>-C<sub>2</sub>)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-45 fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl or 2-iodoethyl; a heterocycle group selected

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from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a

Z = N. O. S or Se

benzo or pyrido ring fused thereto:

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 \cong N. O. S \text{ or Se}$ 

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>3</sub>)alkoxycarbornyl, (C<sub>1</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G-)alkythitopyrdazinyl, or as ix membered saturated ring with so one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-dioxo-1-piperazinyl, 4-ethyl-2-dioxo-1-pipe

Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

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Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, Ithiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-blgyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (Ci-Ca,)alky; C<sub>3</sub>-ary; substituted C<sub>2</sub>-ary! (substitution balc(Ci-Ca)alkoy, thiaba(Ci-Ca)alkoy, thiaba(Ci-Ca)alkoy, althoy, (Ci-Ca)-alky, alky lamino or carboxy); (Ci-C<sub>3</sub>)-aralky! group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl

so such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O, S or Se heteroatoms such as pyridy, pyridaziny, pyraziny), symutriazinyl, unsym-triazinyl, pyrimidinyl or (Ci-Cy)allythilopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 23-dioxo-1-piperazinyl, 4-enthyl-23-dioxo-1-piperazinyl, 4-enthyl-23-dioxo-1-piperazinyl, 4-etyclopropyl-2-dioxo-1-piperazinyl, 4-dioxo-piperazinyl, 4-dioxo-piperazinyl, 4-dioxo-piperazinyl, 4-dioxo-piperazinyl, straight or branched propoxylcatronyl, straight or branched butoxycarbonyl or allyloxycarbonyl, straight or branched propoxylcatronyl, straight or branched butoxycarbonyl or allyloxycarbonyl, vinyl or substituted vinyl group (substitution selected from (Ci-Ca)allyl group, halogen, (Ci-Ca)allyl group selected from phonyl, enaphthyl, 5-aphthyl, substitution (Ci-Ca)allyl group, halogen, (Ci-Ca)allyl group, butyloxycarbonyl, (Ci-Ca)allyl group, substitution selected from halo, (Ci-Ca)allyl group, butyloxycarbonyl, (Ci-Ca)allyl group, butyloxycarbonyl, (Ci-Ca)allyl group, butyloxycarbonyl, (Ci-Ca)allyl group, butyloxycarbonyl, (Ci-Ca)allyl group solected from alloxycarbonyl, difluoromethyl, tribluoromethyl, tribluoromethyl, chiloromethyl, chiloromethyl, chiloromethyl, chiloromethyl, chiloromethyl, chiloromethyl, difluoromethyl, chiloromethyl, chiloromethy

Z = N. O. S or Se

such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, furranyl, benzofuranyl, tetrahydrothenyl, thienyl, benzofuranyl or seienazolylj; (Cr.-Cr.)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or tert-butoxy; Cr-aryloxy

(G--G)alkoxy group such as allyloxy, methoxy, othoxy, n-propoxy, n-butoxy or tert-butoxy; G-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (G--G)alkyl, nitro, cyano, thiol, amino, carboxy, di(G--G-)alkylamino);(G--G-)alralkyloxy group such as benzyloxy, 1-

phonylethyloxy or 2-phenylethyloxy, vinyloxy or substituted vinyloxy group (substitution selected from (Cr-Cr)alkyl, cryano, carboxy, or (Cr-Cr)alkyl selected from phenyl, anaphthyl or β-naphthyly; RPRamino(Cr-Cr)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPR is a straight or branched (Cr-Cr)alkyl, 2 or S; or RPR aminoxy group, wherein RPR is a straight or branched (Cr-Cr)alkyl, 2 or S; or RPR aminoxy group, wherein RPR is a straight or branched (Cr-Cr)alkyl, 6 or S; or -Cr\frac{1}{2}\text{w}(Cr\frac{1}{2}\text{b}, m-2-6, or -Cr\frac{1}{2}\text{w}(Cr\frac{1}{2}\text{b}, m-2-6, or -Cr\frac{1}{2}\text{w}(Cr\frac{1}{2}\text{b}, m-2-6, or -Cr\frac{1}{2}\text{w}(Cr\frac{1}{2}\text{b}, m-2-6), or -Cr\fr

Pt is selected from hydrogen; anino; straight or branched (G--G-)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-bropyl, 1-methylethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylethyl, (G-G-C-)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohoxyl; substituted (G-G-)cycloalkyl group selected from (G--G-)alkyl, cyano, amino or (G--G-)acy); (G--G-)alayl group selected from phenyl, -araphtyl or g-harphtyl); substituted(G-G-G-)aryl group (substitution selected from halo, (G--G-)alkoy, tribacy(G-G-)alkyl, nitro, amino, cyano, (G--G-)alkoycarbonyl, (G--G-)alkylamino or carboxyl; (G-C-)alkoyl group such as bozzyl, 1-phenylethyl, 2-phenylethyl or phenylytorpyl; acylory or haloacyloxy group, selected from acetyl, propionyl, chloroacetyl, trichloroacetyl, (G--G-)cycloalkylcarbonyl, (G--G-)cycloalkylcarbonyl,

Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

36 or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkył-3H-imidazol{,5-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom.

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>4</sub>-aryl; substituted C<sub>4</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoy,carbonyl, (C<sub>1</sub>-C<sub>5</sub>)-alkylamino or carboxy); (C<sub>7</sub>-C<sub>9</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyll

s such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-10 piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy,n-butoxy or tert-butoxy; Cs-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di(C1-C3)alkylamino); (C7-C10)aralkyloxy group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; (C1-C3)alkylthic group selected from methylthio, ethylthio, propylthio or allylthio; Cs-arylthio group selected from phenylthio or 15 substituted phenylthio (substitution selected from halo, (C<sub>1</sub>-C<sub>c</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di-(C<sub>1</sub>-C<sub>3</sub>)alkylamino); C<sub>5</sub>-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl. (C1-C3)alkylamino or carboxy); (C7-C8)aralkylthio group such as benzylthio, 1-phenylethylthio or 2-phenylethylthio; a heterocycle group selected from a five membered aromatic or saturated ring 20 with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benze or pyride rine fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol(1,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N. O,
45 S or So hetoroatoms and an adiacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (G.-C.)alky); C.-aryl; substituted C.-aryl (substitution selected from halo,(C;-C.)alkoxy.crbonyl, (C;-Ca)-alky, nitro, amino, cyano, (C;-C.)alkoxy.carbonyl, (C;-Ca)-alkylamino or carboxy); (C)-C.)alrallyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-

### propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O,S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with 5 one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; hydroxy group; mercapto group; mono- or distraight or branched chain (C<sub>1</sub>-C<sub>6</sub>)alkylamino group selected from methyl, ethyl, n-propyl, 1-methylethyl, nbutyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethyl-10 propyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 1,2dimethylbutyl, 1,3-dimethylbutyl or 1-methyl-1-ethylpropyl amino; (C2-C5)azacycloalkyl group such as aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or 2-methylpyrrolidinyl; carboxy(C2-C4) alkylamino group selected from aminoacetic acid, α-aminopropionic acid, α-aminobutyric acid and their optical isomers; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxyethyl, α-hydroxyethyl or α-hydroxy-1-methylethyl or α-15 hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoromethyl, 2bromoethyl or 2-iodoethyl; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, trifluoroacetyl, (C3-C6)cycloalkylcarbonyl, (C6-C10) aroyl selected from benzoyl or naphthoyl, halo substituted (C<sub>6</sub>-C<sub>10</sub>)aroyl such as pentafluorobenzoyl, 4-chlorobenzoyl, 3-bromobenzoyl, 3,4-difluorobenzoyl, (C<sub>1</sub>-20 C4)alkylbenzoyl such as 4-toluoyl, 2-toluoyl or 4-(1-methylethyl)benzoyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

### Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, luranyl,benzofuranyl, tetrahydrofthenyl, fisienyl, benzoftienyl or selenzacyll, or a five membered aromatic as fing with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

### $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

4s such as imidazo(M, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazol(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ alkoxycarbonyl,  $(C_1-C_3)$ -alkoxycarbonyl,  $(C_1-C_3)$ -alkoxycarbon

alkylamino or carboxy); (C<sub>7</sub>-C<sub>9</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-5 triazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propox-10 yearbonylamino; (C1-C4)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched butoxycarbonyl; RaBamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n=2-6, or -(CH2)2W(CH2)2wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen 15 or (C1-C3)alkyl], O or S; or R®Rbaminoxy group, wherein R®Rb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRo is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl (straight or branched), -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S;

and when  $R = R^4(CH_2)_*SO_2$  and n = 0.

, or

Z = N, O, S or Se

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4s such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, berazhtenyl benzofuranyl, etrahydroflienyl, tilenyl, benzofilenyl or selenazolyl, or a five membered aromatic ring with two N.O. S or Se heterostoms optionally having a benzo or pyrido ring fused filtereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-

alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₁-aryl; substituted C₄-aryl (substitution selected from halo,(C₁-C₄)alkoy, trihalo(C₁-C₄)alkyl, nitro, amino, cyano, (C₁-C₄)alkoycarbonyl, (C₁-C₃) alkylamino or carboxy); (C₂-C₄)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazoildinone or N-aminoimidazoildinone, or a six membered aromatic ring with one to three N. Q. S. or Se heteroatoms such as pyridy, pyridazinyly, pyrazinyl, symutiazinyl, unsym-triazinyl, pyriadinyly or (C.-Cyalkylkhlopyridazinyl, or a six membered salurated ring with one or two N. Q. S. or Se heteroatoms and an adjacent appended O heteroatom such as 2:3-dioxo-1-piperazinyl, 4-etyly-2:3-dioxo-1-piperazinyl, 4-etylp-2:3-dioxo-1-piperazinyl, 4-etylp-2:3-dioxo-1-piperazinyl, 4-etylp-pyriz-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; RPP\*amino(C;-Cyalakyo group, wherein RPP\* is a straight or branched (C;-Cyalaky) selected from methyl, ethyl, n-popyl, 1-methylpropyl or RPP\* is a straight or branched (C;-Cyalaky) selected from methyl, ethyl, n-popyl, 1-methylpropyl or RPP\* is a straight or branched (C;-Cyalakyl) selected from methyl, ethyl, n-popyl, 1-methylpropyl or RPP\* is a straight or branched (C;-Cyalakyl) selected from methyl, ethyl, n-popyl, 1-methylpropyl or 2-methylpropyl or 2-methylpropyl

30 and when R = R4 (CH2)nSO2- and n = 1-4,

A<sup>c</sup> is selected from hydrogen; amino: straight or branched (C,-C, )alkyl group selected from methyl, ethyl, n-propyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylprityl, (C;-C, )carboxyalkyl group; (C3-C, )cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclobaxyl; substituted (C3-Cs, )cycloalkyl group (substitution selected from (C;-C<sub>3</sub>)alkyl, cyano, amino or (C;-C<sub>3</sub>)acyl); (C<sub>3</sub>-C<sub>3</sub>)aryl group (substitution selected from halo, (C;-C<sub>3</sub>)alkylawino, anaphtyl or β-apphtyly; substituted (C3-C3-alkya) group (selected from halo, (C;-C3)alkylawino or actboxy); (C;-C3)arkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; (C;-C3)alkyxy group such as allyloxy, methoxy, ethoxy, n-propoxy or tert-butoxy; C3-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C;-C3)alkyl, nitro, cyano, thiol, amino, carboxy, d((C;-C3)alkylamino);

(C<sub>7</sub>-C<sub>1</sub>-)aralkyloxy group such as benzyloxy, 1-phenylethyloxy or 2-phenylethyloxy; PfPPamino(C<sub>1</sub>-C<sub>4</sub>)-alkoxy group, wherein RfPf is a straight or branched (C<sub>1</sub>-C<sub>4</sub>)-alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methyloptyl, or 2-methyloptyl, or RfPf is (Cf4)-, n=2-6, or (Cf4)-gW(Rf4)-, n=2-6, or (Cf4)-gW(Rf4)-gw wherein W is selected from N(C<sub>1</sub>-C<sub>2</sub>)alkyl (straight or branched), NH, -NDB (B is selected from hydrogen or (Cf-C<sub>2</sub>)-alkyl), or Sic (Cf4)-gw(Rf4)-gw wherein W is selected from PfPf is a straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or PfPf is (Cf4)-gw(Rf4)-gw wherein W is selected from N-NC-C<sub>2</sub>)alkyl (straight or branched), -NDB (B is selected from hydrogen or (C<sub>1</sub>-C<sub>2</sub>)alkyl, 0 or S; (C<sub>1</sub>-C<sub>2</sub>)alkylthio group selected from phenylthio or n-propylthio: C<sub>2</sub>-arylthio group selected from phenylthio or substituted phenylthio (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-c<sub>2</sub>)alkylamino); (C<sub>2</sub>-C<sub>2</sub>)aralkyl thio group such as benzylthio. 1-phenylethylthio or 2-phenylethylthio; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se hetercatom optionally having a beapox or prytich or fig fused thereits.

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Z = N. O. S or Se

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10 such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydroturanyl, turanyl, berizofuranyl, tetrahydrothienyl, thionyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroactoms optionally having, a benzo or pyrdol ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

such as Imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alakyl-3H-Imidazol(4.5-b)pyridyl or pyridyllimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

46 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkxxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkxxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered 40 aromatic ring with one to three N, O,S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C2)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; hydroxy group, mercapto group; mono-or di-45 straight or branched (C<sub>1</sub>-C<sub>6</sub>)alkylamino group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl or 1-methyl-1-ethylpropyl amino; halo(C1-C3)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-50 difluoroethyl, 2,2,2-trifluoroethyl, 2-chloroethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl, 2-bromoethyl or 2iodoethy); acyl or haloacyl group selected from acety), propionyl, chloroacetyl, trifluoroacetyl, (C3-C5)cycloalkylcarbonyl, (C6-C10)aroyl selected from benzoyl or naphthoyl, halo substituted (C6-C10)aroyl such as pentafluorobenzoyl, 4-chlorobenzoyl, 3-bromobenzoyl or 3,4-difluorobenzoyl, (C1-C4)alkylbenzoyl such as 4-toluoyl, 2-toluoyl or 4-(1-methylethyl)benzoyl, or (heterocycle)carbonyl, the heterocycle selected from a 55 five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

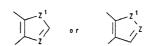


## o Z = N, O, S or Se

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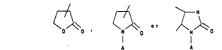
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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofthienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



## $Z \text{ or } Z^1 = N. O. S \text{ or Se}$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-38 alkyl-3t-limidazo(4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent a poended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridy, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (Gr-C<sub>2</sub>)alkythliopyridazinyl, or a six membered saturated ring with 45 one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-ethyty-2.3-dioxo-1-piperazinyl, 4-ethyty-2.3-dioxo-1-piperazinyl, 4-ethyty-2.3-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl group selected from methoxycarbonyl, shboxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched publicxycarbonyl.

50 R<sup>3</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, tG<sub>1</sub>-C<sub>1</sub>-playl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>2</sub>-C<sub>3</sub>)aryl group such as bonzyl, 1-phenylethyl, 2-phenylethyl or phenyltpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se hetercatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se

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such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolidnyl, 3-pyrrolidnyl, 2-pyrrolinyl, tetrahydrofuranyl, to turanyl, benzofuranyl, tetrahydrofinenyl, hitenyl, benzoftienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or } Se$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>4</sub>-aryl; substituted C<sub>4</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoyycarbonyl, (C<sub>1</sub>-C<sub>3</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (G-C-S) alkylthiopyridazinyl, or a six membered saturated ring with 40 one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-enthyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-dibyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-dibyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-dioxomorpholinyl, 2-dioxothiomorpholinyl; or (Ct-B<sub>2</sub>)CODR' where n = 0-4 and R' is selected from from hydrogen; straight or branched (G-C-S)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (Cx-C)alyl group selected from phenyl, a-naphthyl; B\* is selected from 4-byl, a-naphthyl; B\* is selected from thyl, ethyl, n-propyl or 1-methylethyl; cyclopely group selected from phenyl, a-naphthyl; B\* is selected from thyl, ethyl, n-propyl or 1-methylethyl; cyclopely group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a bearco or gyrido ring lysed therator.

### Z = N. O. S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydroturanyl, furanyl, benzoturanyl, tetrahydrotnienyl, thienyl, benzothienyl or selenazolyl, or a five membered arcmaticring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereting.

$$Z^1$$
 or  $Z^1$ 

## $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

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15 such as Imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkly-3H-imidazolyl, 5-bipyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatoms.

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoy,carbonyl, (C<sub>1</sub>-C<sub>2</sub>) alkylamino or carboxyl; (C<sub>7</sub>-C<sub>5</sub>)arakyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as γ-butyrolactam, γ-butyrolactone, imidazoidinone or N-aminoimidazoidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symthazinyl, unsym-triazinyl, pyrimidinyl or (Gr-Cs)alkytithopyridazinyl, or a six membered saturated ring with so one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyt-2,3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-piperazinyl, 4-ethyt-3-dioxo-1-pipe

Preferred compounds are compounds according to the above formula III and IV in which Y is  $NO_2$ ; R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0.

R<sup>4</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>2</sub>)-alkylamino, cyclopropylamino, cyclobutylamino, bencylamino or phenylamino; distustituted amino selected from dimethylamino, distulphamino, ethyl-methylethylymino, monomethylbanzylamino, piperdimyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2.3-triazolyl) or 4-(1,2.4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>3</sub>-C<sub>2</sub>-Cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C<sub>2</sub>-C<sub>3</sub>-Cycloalkyl group (substitution selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, cycno, amino or (C<sub>1</sub>-C<sub>3</sub>-Dalyyl); C<sub>2</sub>-C<sub>3</sub>-Dalyyl group selected from henyl, e-naphthyl or β-naphthyl; cyclopentyl or cyclopenyl, (C<sub>1</sub>-C<sub>3</sub>-Dalkyl); (C<sub>2</sub>-C<sub>3</sub>-Dalkyl); (C<sub>2</sub>-C<sub>3</sub>-Dalkyl); (C<sub>3</sub>-C<sub>4</sub>-Dalkyl); carboxy(C<sub>2</sub>-C<sub>4</sub>-Dalkylamino) selected from henyl, e-aminoethyl, e-aminopropiol or α-aminopropionic acid and their optical isometry (C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) group such as phenylglycyt; (C<sub>1</sub>-C<sub>3</sub>-Dalkoycarbonylamino substitution selected from phenyl or prhydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) group selected from control propertical from phenyl or prhydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) group selected from control propertical from phenyl or prhydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) gelected from phenyl or prhydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) gelected from phenyl or phydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) gelected from phenyl or phydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) gelected from phenyl or phydroxypheny; e-nydroxy(C<sub>2</sub>-C<sub>3</sub>-Dalkylamino) gelected from phenyl or phydroxyphenylamino gelected from phenylamino gelected from phenylamino gele

hydroxymethyl, a-hydroxyethyl or a-hydroxy-1-methylethyl or a-hydroxypropyl; halo(G.-C-)alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, clichoromethyl, c2-burocethyl, 2.2-difluoroethyl, 2.2-burlocethyl, 2.2-difluoroethyl, 2.2-burlocethyl, 2.2-burloc

Z = N, O, S or Se

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1s such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, furanyl, berahydrothinnyl, thinnyl, benzothranyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol(4,5-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alklyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution as selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alklyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>1</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>2</sub>) alkylamino or carboxy); (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered arcmatic ring with one to three N. O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-trazinyl, nwym-trazinyl, pyrimidinyl or (G:-C-)alkylthiopyridazinyl, or a six membered saturated ring with one or two N. O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-emthyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; acyl or haloecyl group selected from acetyl, prepionyl, (c)-C-ca)<sub>2</sub>-aloy selected from benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted from benzoyl or aphthyly, halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted from benzoyl or aphthyly, halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted specified from benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted specified from benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted specified from benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted specified from benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted strom benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted strom benzoyl or aphthyly halo substituted (Ce-Ca)<sub>2</sub>-aloy sleeted strom sleeted should be a second substituted (Ce-Ca)<sub>2</sub>-aloy sleeted strom sleeted should be a second should be a second substituted should be a second should be a s

Z = N, O, S or Se

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such as pyrrolly, N-meithylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, to furanyl, benzofuranyl, benzofuranyl, benzofuranyl, benzofuranyl, benzofuranyl, tetrahydrofuranyl, to furanyl, benzofuranyl, a penzo or pyrido ring fused fibertetic

 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

such as Imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, ithiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N. O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution 35 selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbornyl, (C<sub>1</sub>-C<sub>2</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-dhytly-2-dioxo-1-piperazinyl, 4-drubyl-2-dioxo-1-piperazinyl, 4-drubyl-2-dioxo-1-piperazinyl,

Z = N. O. S or Se

such as pyrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 2-pyrrolidinyl, 2-pyrrolidinyl, 2-pyrrolidinyl, benzoturanyl, tetrahydrothienyl, thianyl, benzothienyl or selenazolyl; (Gr-C<sub>1</sub>)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxyn-butoxy or tert-butoxy; C<sub>2</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (Gr-C<sub>2</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, dt(Gr-C<sub>2</sub>)alkylamino); (Gr-C<sub>1</sub>)alkylamino); (Gr-C<sub>1</sub>)alkylamiloxy (Group such as benzyloxy), r-phenylethyloxy or 2-phenylethyloxy ary selected from phenoxy or Gr-C<sub>2</sub>-phenylethyloxy ary selected from phenoxy or Gr-C<sub>2</sub>-phenylethyloxy ary selected from phenyl, a-naphthyl or A-panhthyl, R-Palmino(Gr-C<sub>2</sub>-plakyl, cyano, carboxy, or (Gr-C<sub>2</sub>-C<sub>1</sub>)) ary selected from phenyl propyl, or z-methylpropyl or PRPs is GCh<sub>2</sub>, in z-26. or (Gr-L<sub>2</sub>), W(Gh<sub>2</sub>)-wherein W is selected from NGCr-C<sub>2</sub>-plakyl (Steright or branched). 4NH. -NOB (B is selected from hydrogen or (Gr-C<sub>2</sub>-plakyl). O or S; or RPPaminoxy group, wherein R-PR is a straight or branched (Gr-C<sub>2</sub>-plakyl). Temblylipylinyl, i-methylpylinyl, or 2-methylpinylyl or R-PRPs is (Gr<sub>2</sub>). The phenyl or R-PR is (Gr<sub>2</sub>) are selected from hydrogen or (Gr-C<sub>2</sub>-plakyl). Or S; or -(Gr<sub>2</sub>-plakyl), Cor S; or -(Gr<sub>2</sub>-plakyl). Or S;

and when  $R = R^4(CH_2)_nCO$ - and n = 1-4.

Pt is selected from hydrogen: (C--C-)alkyl group selected from methyl, athyl, n-propyl or 1-methylethyl; a mino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, distribylamino, benzylamino or phenylamino, propertion, propertion, in the propertion of the propertion



Z = N, O, S or Se

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45 such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } S_{\Theta}$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazol4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O,

S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dloxo-1-20 piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy,n-butoxy or tert-butoxy; RaBamino(C:-Ca)alkoxy group, wherein RaBa is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n = 2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_3)$  alkyl 25 [straight or branched], -NH, -NOB [B is selected from hydrogen or (C -C<sub>3</sub>)alkyl], O or S; or R<sup>3</sup>R<sup>5</sup>aminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n=2-6, or -(CH2)2W(CH2)2wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyll. O or S; C5-aryloxy group selected from phenoxy or substituted phenoxy (substitution 30 selected from halo, (C<sub>1</sub>-C₄)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C₃)alkylamino); (C<sub>1</sub>-C₃)alkylthio group selected from methylthic, ethylthic, propylthic or allylthic; C6-arylthic group selected from phenylthic or substituted phenylthic (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di(C1-C3)alkylamino); C5-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-35 alkoxycarbonyl, (C1-C3)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

## Z = N, O, S or Se

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such as pyrrolyl. N-methylindolyl, indolyl. 2-pyrrolidinyl, 2-pyrrolidinyl, 2-pyrrolidinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothianyl, thianyl, benzothianyl or selenazolyl, or a five membered aromatic so ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused therebs:

$$Z$$
 or  $Z^1 = N$ . O. S or Se

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-b]pyridyl or pyridyllimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

15 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-c<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylproov)!

such as  $\gamma$ -butyrolactam,  $\gamma$ -butyrolactone, imidazelidinone or N-aminoimidazelidinone, or a six membered 20 aromatic ring with one to three N. O.S or Se heteroatoms such as pyriddy, pyridazinyl, symatriazinyl, symatriazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G<sub>2</sub>)alkylthopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-diox-1-piperazinyl, 4-etylcyo-2-dioxo-1-piperazinyl, 4-etylcyo-2-dioxo-1-piperazinyl, 4-etylcyo-pyt-dioxo-1-piperazinyl, 4-etylcyo-pyt-dioxo-1-piperazinyl, 4-etylcyo-pyt-dioxo-1-piperazinyl, 4-etylcyo-pyt-dioxo-2-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; hydroxy group:  $\alpha$ -hydroxyropyl; halo(cl-C<sub>3</sub>)alkyl group selocted from hydroxymethyl,  $\alpha$ -hydroxyethyl or 4-difluoromethyl, filtroormethyl, 2-bromoethyl or 2-iodoethyl; alkyl group such as bromomethyl, fluoromethyl, (Bruoromethyl, 2-bromoethyl or 2-iodoethyl; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, (Gr-C<sub>1</sub>-pixyl such as pentafluorobenzoyl, 4-chlorobenzoyl, 3-bromobenzoyl or 1,4-difluorobenzoyl, (Gr-C<sub>1</sub>-pixyl such as 4-toluoyl, 2-toluoyl, 2-toluoyl, 2-toluoyl, 2-toluoyl, 3-bromobenzoyl or 3,4-difluorobenzoyl, (Gr-C<sub>1</sub>-qixyl such as 4-toluoyl, 2-toluoyl, 2-toluoyl,



## Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

45 or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

## Z or $Z^1 = N$ . O. S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O,

S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo(C<sub>1</sub>-C<sub>2</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>2</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as y-bulyrolactam, y-bulyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (Ci-Ci)-alkylthiopyridazinyl, or a six membered saturated ring with 20 no or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-embtyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cycloponyl-adioxo-1-piperazinyl, actionsomethyl-amino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino;

## 25 and when R = R4 (CH2), SO2 and n = 0.

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R<sup>4</sup> is selected from arino; monosubstituted arinic selected from as straight or branched (c.-C<sub>6</sub>)-alkylamino, cycloputylamino, benzylamino or phanylamino; disbubtituted arino; selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrolyl, 1-1/1,23-friazolyl) or 4-(1,2.4-friazolyl); straight or branched (G.-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-proply or 1-methylethylik (G.-C<sub>3</sub>)alkyl group selected from halo, (C<sub>3</sub>-C<sub>3</sub>)alkoy, ribo, amino, cyano, (G.-C<sub>3</sub>)alkoy, (G.-C<sub>3</sub>)alkylamino or carboxyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom contonally having a benzo cycle.



## Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl,

or a five membered aromatic ring with two N, O, S or Se heteroatorns optionally having a benzo or pyrido ring fused thereto:

## $Z \text{ or } Z^1 = N. O. S \text{ or Se}$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-

alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (G;-C<sub>2</sub>)alkyl; G<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substituted C<sub>3</sub>-aryl (substituted C<sub>3</sub>-aryl) (substituted C<sub>3</sub>-aryl)

such as -y-butyrolactam, -y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridy, pyridaziny, pyrazinyl, symuzov triazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ettlyl-2,3-dioxo-1-piperazinyl, 4-ettlyl-2,3-dioxo-1-piperazinyl, 4-ettlyl-2,3-dioxo-1-piperazinyl, 4-dioxomorpholinyl or 2-dioxomorpholinyl cradioxomorpholinyl cradioxomorp

25 R<sup>4</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>6</sub>)-alk/jamino, cyclopropylamino, cyclobutylamino, shorylamino or phenylamino; distubstituted amino selected from dimethylamino, deltylamino, ethyl-methylethylamino, ethyl-benylamino, pippiedinyl, neropholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-friazolyl) or 4-(1,2-4-friazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkly, group selected from methyl, ethyl, n-propy or 1-methylethyli, (C<sub>2</sub>-C<sub>3</sub>)alyl, group selected from phenyl, an aphthyl or β-naphthyl; substituted (C<sub>4</sub>-C<sub>1</sub>)alxyl group (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkloxy, thialo(G<sub>1</sub>-C<sub>3</sub>)alkly, nitro, amino, cyano, (G<sub>1</sub>-C<sub>2</sub>)alkloxy, strobuloxy or sterbuloxy; C<sub>2</sub>-aryboxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (G<sub>1</sub>-C<sub>3</sub>)alklyl, nitro cyano, thiol, amino, carboxy, 6(C<sub>1</sub>-C<sub>3</sub>)alklyl, mito cyano, thiol, amino, carboxy, 6(C<sub>1</sub>-C<sub>3</sub>)alklyl, mito cyano, thiol, amino seboxy (substitution selected from halo, (G<sub>1</sub>-C<sub>3</sub>)alklyl, nitro cyano, thiol, amino seboxy, for (C<sub>2</sub>-C<sub>3</sub>)alklyloxy group such as benzyloxy, 1-phenylethyloxy.

R<sup>5</sup> is selected from hydrogen: straight or branched (Gr-Cs)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (G<sub>C</sub>-C<sub>0</sub>)ayrl group selected from phenyl, α-naphthyl or β-naphthyl; (Gr-Cs)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or spyrido ring fixed thereto:

## Z = N, O, S or Se

35 or 2-phenylethyloxy; (C<sub>1</sub>-C<sub>4</sub>)carboxyalkyl group;

such as pyrroly!, N-methylindoly!, indoly!, 2-pyrrolidiny!, 3-pyrolidiny!, 2-pyrroliny!, tetrahydrofurany!, urany!,benzofurany!, tetrahydrothieny!, thieny!, benzothieny! or selenazoly!, or a five membered aromatic ring with two N. O. S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

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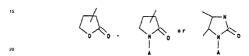
45

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## $Z \text{ or } Z^1 = N. O. S \text{ or } Se$

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10 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl-5-bjpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatoms.



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>) alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as  $\gamma$ -butyrolactam,  $\gamma$ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (Cr-Cs)alkythtopyridazinyl, or a six membered saturated ring with 30 one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-ettyly-2.3-dioxo-1-piperazinyl, 4-ettyly-2.3-dioxo-1-piperazinyl, 4-ettyly-2.3-dioxo-1-piperazinyl, 4-methy-2-dioxo-1-piperazinyl, 4-ettyly-2.3-dioxo-1-piperazinyl, 4-methy-2-dioxo-1-piperazinyl, 4-ettyly-2-dioxo-1-piperazinyl, 4-methy-2-dioxo-1-piperazinyl, 4-piperazinyl, 4-giby-2-dioxo-1-piperazinyl, 4-methy-2-dioxo-1-piperazinyl, 4-methy-2-d

58 R<sup>3</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, repropyl or 1-methylethyl; (C<sub>2</sub>-C<sub>1</sub>-C<sub>1</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>2</sub>-C<sub>2</sub>-plaralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

### Z = N. O. S or Se

such as pyrrolly, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrolluranyl, 50 furanyl, benzofuranyl, tetrahydrollinenyl, filenyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyriod ring fused thereto:

## Z or $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol(4,5-b)pyridyl or pyridylimidazoly, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

16 (A is selected from hydrogen; straight or branched (G.-Ca,lalkyl; Co-ray); substituted C<sub>x</sub>-ary) (substituted selected from halo,(G.-Ga)lalkov, hiraled(G.-Ga)lalkov, narino, cyano, (G.-Ca)lalkov, atrabed(G.-Ga)lalkov, arrino, cyano, (G.-Ca)lalkov, atrabed (G.-Ga)lalkov, atrabed (G.-Ga)lalkov

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatoms such as pyridyl, pyridazinyl, symtrazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxot-piperazinyl, 4-enthyl-2-3-dioxot-piperazinyl, 4-enthyl-2-3-dioxot-piperazinyl, 4-enthyl-2-3-dioxot-piperazinyl, 4-enthyl-2-3-dioxot-piperazinyl, 2-dioxompholinyl, 2-dioxothiomorpholinyl; or (CH<sub>2</sub>)<sub>0</sub>COOR<sup>2</sup> where n = 0-4 and R<sup>2</sup> is selected from methyl, ethyl, n-propyl or 1-methylethyl; or (Gc-C<sub>2</sub>-G<sub>2</sub>)aryl selected from phenyl, a-napthyl or β-napthyly, with the proviso that R<sup>2</sup> and R<sup>2</sup> cannot both be

or R<sup>5</sup> and R<sup>5</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n=0-1, -NH, -N-(Cr-C<sub>2</sub>)alky [straight or branched]. -N(Cr-C<sub>3</sub>)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Particularly preferred compounds are compounds according to the above formula III and IV in which Y is NO<sub>2</sub>:

R is selected from R4 (CH2), CO- or R4 (CH2), SO2-;

35 and when R = R4 (CH2)nCO- and n = 0, R4 is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C1-C6)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, t-imidazolyl, t-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(t,2,4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl 40 group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C3-C6)cycloalkylgroup selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>5</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or βnaphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl. nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); α-amino-(C<sub>1</sub>-C<sub>4</sub>)alkyl group 45 selected from aminomethyl, α-aminoethyl, α-aminopropyl or α-aminobutyl; carboxy(C<sub>2</sub>-C<sub>4</sub>)alkylamino group selected from aminoacetic acid, a-aminobutyric acid or a-aminopropionic acid and their optical isomers; (C<sub>7</sub>-C<sub>9</sub>)aralkylamino group such as phenylglycyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino substituted (C<sub>1</sub>-C<sub>4</sub>)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy+t-methylethyl or α-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group such 50 as bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl or 2-iodoethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N. O. S or Se

10 such as pyrrolyi, N-methylindolyi, indolyi, 2-pyrrolidnyi, 3-pyrrolidnyi, 2-pyrrolinyi, tetrahydrofuranyi, furanyi, benzofuranyi, tetrahydrofuranyi, tetrahydrofuranyi, benzofuranyi, benzofuranyi, tetrahydrofuranyi, benzofuranyi or selenazolyi, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or  $Z^1 = N$ , O, S or Se

benzo or pyrido ring fused thereto:

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alw/SH-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, 25 S or Se heteroatoms and an adjacent appended O heteroatom:

35

30

20

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)-alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as 7-butyrolactam, 7-butyrolactone, imidazoldinone or N-aminoimidazolidinone, or a six membered aromatic, ring with one to three N. O. S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symthazinyl, unsym-triazinyl, pyrimidinyl or (Cr-C<sub>2</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-diox-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-ethyl-2-3-dioxo-1-piperazinyl, 4-cytoporyl-2-dioxol-piperazinyl, 4-g-tytoporyl-2-dioxol-piperazinyl, 4-cytoporyl-2-dioxol-piperazinyl, (Cy-Cyloravyl-2-dioxol-piperazinyl, 4-cytoporyl-2-dioxol-pyl, (Cy-Cyloravyl-2-dioxol-pyl), (Cy-Cyloravyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-dioxol-pyl-2-di

 $Z \approx N, O, S \text{ or Se}$ 

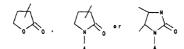
15

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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, turanyl, bertzofuranyl, tetrahydrofurienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

20 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl, 5-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or S6 heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₂)alky); C₄-aryl; substituted C₄-aryl (substitution selected from halo,(C₁-C₂)alkoy, rithalo(C₁-C₂)alkoy, nitro, amino, cyano, (C₁-C₂)alkoy,carbonyl, (C₁-C₃)alkoy,carbonyl, (C₁-C₃)alkoy); (Cィ-C₃)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as 7-butyrolactam, 7-butyrolactone, imidazoldinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatoms such as pyridyl, pyridazinyl, symtiazinyl, unsym-triazinyl, pyrimidinyl or (Ci-Ci-pilekythiopyridazinyl, or a six membered saturated ring with an one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-embtyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-3-dioxo-1-piperazinyl, 4-methyl-2-dioxo-piperazinyl, 4-methy

Z = N. O. S or Se

5

10 such as pyrröyl, N-methylindolyl, Indolyl, 2-pyrrolidinyl, 2-pyrrolidinyl, 2-pyrrolidinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofthienyl, thienyl, benzofthienyl or selenazolyl]; (G-G-Jalkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy,n-butoxy or terl-butoxy; C<sub>4</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (Gr-G-Jalkyl, nitro, cyano, thiol, amino, carboxy, diff-(2-)alkylaminol)(Gr-G-Ia)arklydroxy group such as benzyloxy, 1-phenylethyloxy or 52-phenylethyloxy group such as benzyloxy, 1-phenylethyloxy, or substituted vinyloxy group (substitution selected from (Gr-G-Jalkox) group, carboxy, or (G-G-Ia)arkly selected from phenyl, α-naphthyl or β-naphthyli, RPPaimino(Gr-Galkoxy group, wherein RPR is a straight or branched (Gr-G-Jalky) selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPR is (Gr-Dalky), n-2-6, or (G-Dalkyl) selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethylethyl, n-butyl, 1-methylethyl, n-b

and when R = R\*(Cht<sub>2</sub>),CO<sub>2</sub> and n = 1-4, 2s R¹ is selected from methyl, ethyl, n-propyl or 1-methylethyl; amino; monosubstituted amino selected from straight or branched (G;-G; alkylamino, cyclobrylamino, benzylamino or phenylamino; distributed amino selected from distributed amino selected from distributed amino selected from distributions, diethylamino, benzylamino or phenylamino; distributed amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-proyl, 1-ft.(2.S-ftazolyl) of 4ft.2-ftriazolyl); (G;-G;) pally given selected from halo, (G;-G;-G);-g) paryl group, substitution selected from halo, (G;-G;-G);-g) paryl selected from acetyl, propolnyl, chirolocaectyl, (G;-G;-G;-G);-g) paryl selected from benzoyl or naphthoyl, halo substituted (G;-G;-G;-G);-g) substituted (G;-G;-G;-G;-G);-g) paryl selected from benzoyl or naphthoyl, halo substituted (G;-G;-G;-G;-G);-g) and selected from benzoyl or naphthoyl, halo substituted (G;-G;-G;-G;-G;-G;-G;-G);-g) revised from the distribution of the



Z = N, O, S or Se

40

55

45 such as pyrrolly. N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollnyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydroftnenyl, thienyl, benzoftnenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O,

S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo.(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyll

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C2)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-20 piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or tert-butoxy; Co-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C1-C4)alkyl,nitro, cyano, thiol, amino, carboxy, di(C1-C3)alkylamino); R8Rb amino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, 25 n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R<sup>a</sup>R<sup>b</sup> is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W-(CH2)2- wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl, O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n = 2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_3)$ alkyl [straight or 30 branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; (C<sub>1</sub>-C<sub>3</sub>)alkylthio group selected from methylthio, ethylthio, propylthio or allylthio; C6-arylthio group selected from phenylthio or substituted phenylthic (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di-(C1-C3)alkylamino); C6-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)-35 alkoxycarbonyl, (C1-C3)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring one N. O. S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



## Z = N, O, S or Se

such as pyrrollyl. N-melthylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrolldinyl, 2-pyrrollnyl, letrahydrofuranyl, of furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzofhienyl or selenazolyl, or a five membered aromatic ring with two N, O,S or Se heterostoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

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10 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl, b-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C₁-C₂)alkyl; C₂-aryl; substituted C₂-aryl (substitution selected from halo,(C₁-C₂)alkoxy, trihalo(C₁-C₂)alkyl, nitro, amino, cyano, (C₁-C₂)alkoxycarbonyl, (C₁-C₂)alkylamino or carboxyl; (C₂-C₂)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as --butyrolactam, --butyrolactone, imidazolidinone or N-aminolmidazolidinone, or a six membered aromatic ring with one to three N. Q.S. or Se heteroatens such as pyridy, pyridaziny, pyraziny, symptriazinyl, unsym-triazinyl, pyriaminyl, pyriaminyl, pyrazinyl, symptriazinyl, unsym-triazinyl, pyriaminyl, pyrazinyl, symptriazinyl, unsym-triazinyl, pyrazinyl, symptriazinyl, aromatoryl, aromatoryl,

## Z = N, O, S or Se

45

so such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydroturanyl, furanyl, benzofuranyl, tetrahydrothianyl, thinnyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto;

## Z or Z1 = N, O, S or Se

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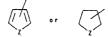
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

15 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as 7-bulyrolactam, 7-bulyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtiazinyl, unsym-triazinyl, pyrimdinyl or (Cr-C<sub>2</sub>)alkylthlopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl (Cr-C<sub>4</sub>)alkoxycarbonylamino group selected from technology-lamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino.

# and when $R = R^4(CH_2)_nSO_2$ - and n = 0,

R<sup>6</sup> is selected from arino; monosubstituted arino selected from as straight or branched (c,-C<sub>6</sub>)-alloylarino, cyclopotyylarino, peralylarino or penylarino; disubstituted arino; selected or form dimethylarino, cyclopotyylarino, ethyl(1-methylethyl)arino, monomethylbenzylarino, piperdinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,23-triazolyl) or 4-(1,24-triazolyl); straight or branched (c<sub>1</sub>-C<sub>9</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>2</sub>-C<sub>9</sub>)alyr) group selected from phenyl, anaphthyl or β-naphthyl; substituted (C<sub>2</sub>-C<sub>19</sub>)arvy) group (substitution selected from halo, (C<sub>1</sub>-C<sub>9</sub>)alkovy; trihalk(C<sub>1</sub>-C<sub>9</sub>)alkyl, ritor, amino, cyano, (C<sub>1</sub>-C<sub>9</sub>)alkovy; (C<sub>1</sub>-C<sub>9</sub>)alkyminion or carboxyl; a heterocycle or group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ing lased thereto:



### Z = N. O. S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofhianyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido fing fused theretoatoms optionally having a benzo or pyrido fing fused theretoatoms optionally having a benzo or pyrido fing fused theretoatoms optionally having a benzo or pyrido fing fused theretoatoms optionally having a benzo or pyrido fing fused theretoatoms optionally having a benzo or pyrido fing fused fused fundamental fundamen

## $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended 0 heteroatom:

15 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo,(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-proov)

such as y-butyrolactam, y-butyrolactone, imidazoidinone or N-aminoimidazoidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridy, lydiadzinyl, pyracinyl, syntriazinyl, unsym-triazinyl, pyrimidinyl or (Cir-C<sub>2</sub>)alkylthlopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl control programments.

## 25 and when R = R4 (CH2), SO2- and n = 1-4,

R<sup>4</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (c.-C<sub>6</sub>)-alkylamino, cyclopropylamino, cyclopropylamino penzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylathy)amino, monomethylbenzylamino, piperidinyl, mornomethylbenzylamino, selected from methylbenzylamino, wherein RPR is a straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylpethyl, n-bulyl, 1-methylpethyl, n-bulylpethyl, n-bulylpethylpethyl, n-bulylpethyl, n-bulylpethyl, n-bulylpethylpethyl, n-bulylpethylpethyl, n-bulylpethylpethylpethyl, n-bulylpethylpethylpethyl, n-bulylpethylpethyl, n-bulylpethylpethylpethyl, n-bulylpethylpethyl, n-bulylpethylpethylpethyl, n-bulylpethylpethylpethyl, n-bulylpethylpethylpethyl, n-bulylpethylpethyl, n-bulylpethylpethylpethylpethylpethylpethylpethyl, n-bulylpethylpethyl, n-bulylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethylpethyl

R<sup>5</sup> is selected from hydrogen; straight or branched (Ch-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>2</sub>-C<sub>3</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>2</sub>-C<sub>3</sub>)aralkyl group auch as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

## Z = N, O, S or Se

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such as pyrrolly, N-melhylindolyl, indolyl, 2-pyrrolldnyl, 3-pyrrolldnyl, 2-pyrrollnyl, tetrahydrofuranyl, 5 furanyl, benzofuranyl, tetrahydrothlenyl, thlenyl, benzothlenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or  $Z^1 = N$ . O. S or Se

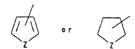
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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl, 5-bjpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacont appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-G<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(G<sub>1</sub>-G<sub>4</sub>)alkoy, trihalo(G<sub>1</sub>-G<sub>3</sub>)alkyl, nitro, artino, cyano, (G<sub>1</sub>-G<sub>4</sub>)alkoy,carbonyl, (G<sub>1</sub>-G<sub>3</sub>) alkylamino or carboxy); (G<sub>7</sub>-G<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as ¬-butyrolactam, ¬-butyrolactone, Imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridy, pyridazinyi, pyracinyi, sym-triazinyi, pyrimdinyi or (Gr-G<sub>2</sub>)alkythtopyridazinyi, or a six membered saturated ring with 30 one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyi, 4-embtyl-2-dioxo-1-piperazinyi, 4-embt

38 Pf is selected from hydrogen: straight or branched (G-Cs)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (G-Cs)alyl group selected from phenyl, --naphthyl or ß-naphthyl; (G-Cs)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fixed therefor.



# Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofuranyl, thienyl, benzofurienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

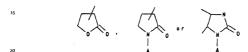
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Z or  $Z^1 = N$ , O, S or Se

10 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-bjpyfdyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>2</sub>-aryl; substituted C<sub>2</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoyycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtazinyl, unsym-triazinyl, pyrimidinyl or (C<sub>1</sub>-C<sub>2</sub>)alkythtopyridazinyl, or a six membered atturated ring with so one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-enthyl-23-dioxo-1-piperazinyl, 4-

or R<sup>2</sup> and R<sup>4</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>, W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n = 0-1, -NH, -N-(C<sub>1</sub>-C<sub>2</sub>)alkyl [straight or branched], -N(C<sub>1</sub>-C<sub>4</sub>)alkovy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)proline, morpholine, pyrolidine or piperidine; and the pharmacologically acceptable oragin and incroanic salts or metal complexes.

Most particularly preferred compounds are compounds according to the above formula III and IV in which Y is NO<sub>2</sub>;

R is selected from R<sup>4</sup> (CH<sub>2</sub>)<sub>n</sub>CO- or R<sup>4</sup> (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-;

and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R¹ is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (G·-G<sub>2</sub>)alkylamino, cyclopropylamino, evploativitamino enpalyamino; dispublituted amino selected
from dimethylamino, cyclopropylamino, enpalyamino, monomethylamino, injendinyl, morpholinyl, 1-midazoyl, 1-pyrolyl, 1-f(2-3-frazoyl) or 4-f(1-2-4-frazoyl); straight or branched (G·-C<sub>2</sub>)alkyl
group selected from methyl or ethyl; (G<sub>2</sub>-C<sub>1</sub>)anyl group selected from phenyl, e-naphthyl or β-naphthyl;
so amino, cyano, (G·-C<sub>2</sub>)alkylographonyl, (G·-C<sub>2</sub>)alkylamino or carboxy); carboxy(C<sub>2</sub>-C<sub>2</sub>)alkylyminio group selected from monometric acid and their optical isomers; ahydroxyp(G·-C<sub>2</sub>)alkylographonyl, (G·-C<sub>2</sub>)alkylamino or carboxy); carboxy(C<sub>2</sub>-C<sub>2</sub>)alkylyminio group selected from horizonymetryl, -hydroxyetryl or -hydroxyetryl or -hydroxyetrylographonyl,
for-C<sub>2</sub>)alkyl group selected from hydroxymetryl, -hydroxyetryl or -hydroxyetryl or -hydroxyetryl or -hydroxyetryl consentlyl, itiliucorentlyl, 2-florometryl, carboxyetryl, 2-florometryl, carboxyetryl, carb

#### Z = N, O, S or Se

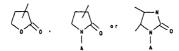
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10 such as pyrroliy, N-methylindolyl, indolyl, 2-pyrrolidnyl, 3-pyrrolidnyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrothrienyl, thienyl, benzofutenyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

#### $Z \text{ or } Z^1 = N. O. S \text{ or Se}$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3adkyl-3H-imidazo(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O,
25 S or So heteroatoms and an adjacent appended O heteroatom:



- 35 (A is selected from hydrogen; straight or branched (C₁-C₂)alkyl; C₄-aryl; substituted C₄-aryl (substitution selected from halo,(C₁-C₂)alkoy, trihalo(C₁-C₂)alkyl, nitro, amino, cyano, (C₁-C₂)alkoxycarbonyl, (C₁-C₂)alkylamino or carboxy); (C₁-C₄)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)
- such as y-butyrolactam, y-butyrolactone, imidazoldinone or N-aminoimidazolidinnee, or a six membered aromatic ring with one to three N. O. S or Se heteroatome such as pyridyl, pyridazinyl, pyrazinyl, symitazinyl, unsym-triazinyl, pyrimidinyl or (Ci-C<sub>2</sub>)alkythtopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatomes and an adjacent appended O heteroatom such as 2,3-diox-1-piperazinyl, 4-enthyl-2,3-dioxo-1-piperazinyl, 4-enthyl-2,3-dioxo-1-piperazinyl,4-enthyl-2,3-dioxo-1-piperazinyl,4-enthyl-2,3-dioxo-1-piperazinyl,4-enthyl-2,3-dioxo-1-piperazinyl,4-enthyl-2,3-dioxo-1-piperazinyl,4-enthyl-2,3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-piperazinyl,4-enthyl-3-dioxo-1-pipe

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thereto:

Z = N, O, S or Se

such as pyrrolyi. N-mathylindolyi. Indolyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 2-pyrrolidinyi. 3-pyrrolidinyi. 3-pyrrolidinyi.

and when  $R = R^4(CH_2)_nCO$ - and n = 1-4,

R¹ is selected from hydrogen; (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl; amino; monosubstituted sa mino selected from straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkylamino, cycloburylamino, cycloburylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, dehylamino, ethylique amino selected from dimethylamino, dehylamino, ethylique amino selected from plant, an-aphthyl, 1-pyrroly, 1-(1,2.3-trazoly) or 4-(1,2.4-frazylamino, dehylamino, ethylique or 4-(1,2.4-frazylamino, ethylique or 4-(1,2.4-frazylamino) or 3-(1,2.3-frazylamino) or 3-(1,



Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrofuranyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms opionally having a benzo or pyrido ring fused therefore.



#### Z or $Z^1 = N$ , O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol/4,5-blpyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adiacent appended O heteroatom:

15 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alky); C<sub>5</sub>-ary); substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>2</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alky), nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)akoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyloroovil)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N, O, S or Se heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (C1-C3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1piperaziny), 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1piperazinyl, 2-dioxomorpholinyl or 2-dioxothiomorpholinyl; (C1-C4)alkoxy group such as allyloxy, methoxy, 25 ethoxy, n-propoxy, n-butoxy or tert-butoxy; RaRbamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2methylpropy) or RaRb is (CH2)n, n = 2-6, or -(CH2)2W(CH2)2- wherein W is selected from -N(C1-C3)alky) (straight or branched), -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-30 methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl],O or S; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or αhydroxy-1-methylethyl or a-hydroxypropyl; halo(C1-C3)alkyl group such as bromomethyl, fluoromethyl, difluoromethy), trifluoromethy), chloromethy), dichloromethy), trichloromethy), 2-fluoroethy), 2,2-difluoroethy), 35 2,2,2-trifluoromethyl, 2-bromoethyl or 2-iodoethyl; (C1-C4)alkoxycarbonylamino group selected from tertbutoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino:

# and when $R = R^4(CH_2)_nSO_2$ - and n = 0,

R<sup>4</sup> is selected from amino; monosubstituted amino selected from as straight or branched (G·-C<sub>2</sub>)-alkylamino, cyclopropylamino, percylamino pencylamino or phenylamino; disubstituted amino selected from dimethylamino, cyclopropylamino, percylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylathyl)jamino, monomethylbenzylamino, piparidinyl, morpholinyl, 1-initiazolyl, 1-pyrrolyl, 1-(1,2-3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (G·-C<sub>2</sub>)alkyl group selected from phenyl, a-raphthyl or β-naphthyl or group selected from phenyl, a-raphthyl or β-naphthyl, and phenyl group selected from phenyl, a-raphthyl or β-naphthyl, and phenyl group (G·-C<sub>2</sub>)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

#### Z = N, O, S or Se

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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl,

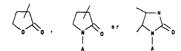
furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or Se}$ 

10

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3algo/3H-imidazol(4,5-b)pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O,

5 or Se Heronatoms and an adiazent appended D heteroratom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₄-aryl; substituted C₄-aryl (substitution selected from halo,(C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₂-C₂)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as 7-butyrolactam, 7-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatoms such as pyrioti, privaiazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (Gr-G-)alkylthiopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl. 4-ethyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl or 2-dioxothio-morpholinyl;

and when  $R = R^4 (CH_2)_n SO_2$  and n = 1-4,

R<sup>4</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl;
R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl
or 1-methylethyl; (C<sub>2</sub>-C<sub>2</sub>)aryl group selected from prenyl, -n-apthyl or -n-apthyliv; (C<sub>2</sub>-C<sub>2</sub>)arakyl group
such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five
membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or
pyrido ring fused therefor.



Z = N, O, S or Se

such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto.

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Z or  $Z^1 = N$ , O, S or Se

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an

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-10 alkyl-3H-imidazo(1,5-b)pyndyl or pyndylimidazolyl, or a five membered saturated ring with one or two N, O, S or So heteroatoms and an adiacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alky); C<sub>5</sub>-ary); substituted C<sub>4</sub>-ary) (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alky), ritiro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoyycarbony), (C<sub>1</sub>-C<sub>5</sub>)aralkyl group selected from benzy), 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N. O. S or Se heteroatoms such as pyridity, pyridazinyl, pyrazinyl, symthazinyl, unsymthazinyl, pyrimidinyl or (Cir-C<sub>2</sub>)alky/thtopyridazinyl, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom such as 2.3-dioxo-1-piperazinyl, 4-entryl-2.3-dioxo-1-piperazinyl, 4-methyl-2.3-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 2-dioxomorpholinyl, 3-dioxomorpholinyl, or -(Ct-b<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl, or (Cx-C<sub>2</sub>)alkyl group selected from phenyl, a-maphtyl, β-naphtyl, β-naphtyl,

R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>2</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, -p-popyl or 1-methylethyl; (C<sub>2</sub>-C<sub>1</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>2</sub>-C<sub>3</sub>)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pvrido ring fixed thereto:

Z = N, O, S or Se

such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolldinyl, 2-pyrrolldinyl, 2-pyrrollnyl, tetrahydroturanyl, ofuranyl, benzofuranyl, tetrahydrothienyl, thinnyl, benzofhienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

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such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3alkyl-3H-imidazol4,5-blgyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

15 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, arnino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyl-propyl)

such as y-butyrolactam, y-butyrolactone, imidazoldinone or N-aminoimidazolidinone, or a six membered a aromatic ring with one to three N. Q. S or Se heteroatmos such as pyridyl, pyridazinyl, pyrazinyl, symtriazinyl, unsym-triazinyl, pyrimidinyl or (Ci-C<sub>3</sub>)alkylthiopyridazinyl, or a six membered saturated ring with one or two N. Q. S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piporazinyl, 4-enthyl-2,3-dioxo-1-piporazinyl, 4-methyl-2,3-dioxo-1-piporazinyl, 4-drophyl-2-dioxo-1-piporazinyl, 4-

(G<sub>\*</sub>-C<sub>10</sub>)ary) solected from phenyl, σ-naphthyl or β-naphthyl; with the proviso that R<sup>2</sup> and R<sup>2</sup> cannot both be hydrogen: or R<sup>2</sup> and R<sup>2</sup> taken together are -{CH<sub>2</sub>}<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>8</sub> and n = 0-1, -NH, -N-(C<sub>1</sub>-C<sub>2</sub>)alkroy, oxygen, sulfur or substituted congeners selected from (G L or Diprofile, ethyl (L or Diprofile, ethyl (L or Diprofile, ethyl (L or Diprofile, ethyl (L or Diprofile).

acceptable organic and inorganic salts or metal complexes.

Compounds of special interest are compounds according to the above formula III and IV in which Y is

R is selected from R<sup>4</sup>(CH<sub>2</sub>)<sub>n</sub>CO- or R<sup>4</sup>(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-;

35 and when R = R\*(CH<sub>2</sub>)<sub>n</sub>CO- and n = 0,

 $\mathbb{R}^4$  is selected from hydrogen; straight or branched ( $\mathbb{C}_1$ - $\mathbb{C}_2$ )alkyl group selected from methyl or ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, or S heteroatton optionally having a benzo or pyrido ring fused thereto:

or or

Z = N. O or S

so such as pyrrollyi, N-methylindolyl, indolyl, 2-pyrrolldinyl, 3-pyrrolldinyl, 2-pyrrollnyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

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an

$$\downarrow$$

 $Z \text{ or } Z^1 = N. O. \text{ or } S$ 

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re such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazolyl, 5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O or S heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C1-C2)alkyl; C6-aryl)

28 such as s-putyrolactam, y-butyrolactone, imidazoidinone or N-aminoimidazoidinone; (C,-C<sub>4</sub>)alkovy-carbony) group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxykarbonyl, straight or branched propoxykarbonyl, straight or branched propoxykarbonyl, straight or branched propoxykarbonyl, straight or (C<sub>1</sub>-C<sub>2</sub>)alkyl group, (C<sub>2</sub>-C<sub>1</sub>)alyl group selected from phonyl, a-naphthyl, β-naphthyl, β-naphthyl, substitution selected from phonyl, a-naphthyl, β-naphthyl, substitution selected from phonyl, a-naphthyl, β-naphthyl, global proposed p

40 R4 is selected from hydrogen; (C1-C2)alkyl group selected from methyl or ethyl; amino; monosubstituted amino selected from straight or branched (C1-C6)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, or 1-(1,2,3triazolyl);  $(C_6-C_{10})$ aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl; substituted $(C_6-C_{10})$ aryl group 45 (substitution selected from halo, (C1-C4)alkoxy, nitro, amino, (C1-C4)alkoxycarbonyl); acyloxy or haloacyloxy group selected from acetyl, propionyl or chloroacetyl; (C1-C4)alkoxy group such as allyloxy, methoxy, ethoxy, n-propoxy, n-butoxy or tert-butoxy; RaRbamino(Ci-Ci)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl 50 [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2 W(CH2)2wherein W is selected from -N(C<sub>1</sub>-C<sub>2</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or  $(C_1 - C_3)$ alkyl], O or S; halo $(C_1 - C_3)$ alkyl group such as bromomethyl, fluoromethyl, difluoromethyl, 55 trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2-difluoroethyl, 2,2-difluoroethyl, 2,2,2trifluoromethyl, 2-bromoethyl or 2-iodoethyl; (C1-C4)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonvlamino:

and when  $R = R^4(CH_2)_nSO_2$  and n = 0,

R<sup>d'</sup> is selected from straight or branched (C--C<sub>2</sub>)alkyl group selected from meltryl or athyl; (C<sub>2</sub>-C<sub>1</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>2</sub>-C<sub>1</sub><sub>0</sub>)aryl group (substitution selected from halo, (C<sub>1</sub>-C<sub>1</sub>)alkoy, nitro, (C<sub>1</sub>-C<sub>2</sub>)alkoy, nitro, (C<sub>1</sub>-C<sub>3</sub>)alkoy, nitro, (C<sub>1</sub>



Z = N. O. S or Se

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such as pyrrollyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolldinyl, 2-pyrrolinyl, tetrahydrofuranyl, turanyl, benzofuranyl, tetrahydrofurienyl, thienyl, benzofulenyl or selenazolyl, or a five membered aromatic in



 $Z \text{ or } Z^1 = N, O \text{ or } S$ 

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkly-3H-imidazol,5-b)pyridyl or pyridylimidazolyl; and when R = Rf (CH-5,00>- and n = 1-0.

R4 is selected from hydrogen; straight or branched (C1-C2)alkyl group selected from methyl or ethyl;

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl

R<sup>6</sup> is selected from hydrogen; straight or branched (C₁-C₂)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R<sup>6</sup> and R<sup>6</sup> cannot both be hydrogen;

or R<sup>s</sup> and R<sup>s</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n = 0-1, -NH, -N-(Gr-G<sub>2</sub>)alkly [straight or branched], -NG-G<sub>2</sub>)alkoxy, oxygen, sulfur or substituted congeners selected from (L or O)proline, ethyl(L or O)prolinate, morpholine, pyrrolidine or piperidine;and the pharmacologically acceptable organic and inorganic salts or metal complexes.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The novel compounds of the present invention may be readily prepared in accordance with the following schemes.

The starting 7-(substituted amino)-6-demethyl-6-deoxyletracyclines described in formula 1, wherein  $X = NR^1R^2$  and  $R^1 = R^2$  (1a) and  $X = NR^1R^1$  (1b) or the salts thereof are prepared by procedures known to those skilled in the art including those described in U.S. Patents 3,226,436 and 3,518,306.

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1a. x = NR<sup>1</sup>R<sup>2</sup>, R<sup>1</sup> = R<sup>2</sup>

1b. x = NHR1

 $\overline{1c}$ , x = NR<sup>1</sup>R<sup>2</sup>, R<sup>1</sup>  $\neq$  R<sup>2</sup>

The starting  $^7$ -(substituted amino)-6-demethyl-6-deoxytetracyclines described in formula 1 wherein  $X=NR^1R^2$  and  $R^1=R^2$  (1c) are prepared according to Scheme 1.

#### Scheme 1

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In accordance with Scheme 1, a 7-(monoalkylamino)-6-demethyl-6-deoxytetracycline, 1b,in which X = NHR1, is reductively alkylated with an aldehyde to give an unsymmetrical dialkylamino, 1c.

### Scheme II

In accordance with Scheme II, a 7-(substituted amino)-6-demethyl-6-deoxytetracycline or its salts, 1a or 1c, is treated with

 a) a metal nitrate salt; such as calcium, potassium or sodium; and a strong acid; such as sulfuric acid, trifluoroacetic acid, methanesulfonic acid or perchloric acid or

 b) nitric acid and a strong acid; such as sulfuric acid, trifluoroacetic acid, methanesulfonic acid or perchloric acid; to form the corresponding 7-(substituted amino)-9-nitro-8-demethyl-8-deoxytetracycline

To produce the 9-(anino)-7-(substituted amino)-6-demethyl-6-deoxytetracyclines. 3, compound 2 or its salts is treated with hydrogen in an acidic alcohol solvent, in the presence of a suitable catalyst such as, for sexample: a) any supported catalyst; such as 0.5-23% palladium-on-carcino,0.5-25% palladium-

Alternatively, the 9-(amino)-7-(substituted amino)-6-demethyl-6-deoxytetracyclines, 3, are obtained by treating with:

a) stannous chloride dihydrate as described by R. B. Woodward, Org. Syn., Coll. Vol. 3, 453 (1955);

b) a soluble metal sulfide, preferably sodium sulfide, in alcoholic solvents as described by G. R. Robertson, Org. Syn., Coll. Vol. 1, 52 (1941);

c) an active metal in mineral acid; such as iron, tin or zinc in dilute hydrochloric acid;

d) active metal couples; such as copper-Zinc, tin-mercury or aluminum amalgam in dilute acid; or

e) transfer hydrogenation using triethylammonium formate and a supported catalyst as described by I. D. Entwistle et al., J. Chem. Soc., Perkin 1, 443 (1977).

Preferably, the 9-(amino)-7-(substituted amino)-6-demethyl-6-deoxytetracyclines 3, are obtained as inorganic salts such as hydrochloric, hydrotromic, hydrolodic, phosphoric, nitric or sulfate.

### SCHEME III

#### SCHEME III

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In accordance with Scheme III, a 9-(amino)-7-(substituted amino)-6-demethyl-6-deoxytetracycline or its salts, 3, is treated with an acyl chloride, acyl anhydride, mixed acyl anhydride, sulfonyl chloride or sulfonyl anhydride in the presence of a suitable acid scavenger in a variety of solvents to form the corresponding 9- (acyl or sulfonyl amino)-7-(substituted amino)-6-demethyl-6-deoxytetracycline, 4. The acid scavenger is selected from sodium bicarbonate, sodium acetate, pyridine, firethylamino, No-Dist(imterbylsi)/plactlamide, NO-bis(trimethylsily)/bir(horoacetamide or a basic ion-exchange resin. The solvents are selected from 3s water-letrahydroluran, N-methylpyrrolidone, 1,3-dimethyl-2-limidazolidione, hexamethylphosphoramide, 1,3-dimethyl-3-4,5-fletrahydro-2(11)-pyrimidione or 1,2-dimethyl-2-throxytethane.

Alternatively, in accordance with Scheme III, a 9-(acytamino)-6-damethyl-6-deoxyletracycline, Sa, prepared by the procedures described in U.S. Patent 3:239,490, or a 9-(sulfonylamino)-6-demethyl-6-deoxy yletracycline, Sb, prepared by the procedures described in this invention, is treated with a halogenation 40 agent such as Toronine, N-toromoacetamide, N-toromoscuccinimide, iodine monochloride, benzyltrimethylammonium chioride lodine monochloride complex or N-todosuccinimide to give the corresponding 9-(acyt or sulfonylamino)-7-halo-6-demethyl-6-deoxyletracycline, 6. Similarity, compound Sa or Sbc an be troated with:

a) a metal nitrate such as calcium, potassium or sodium; and a strong acid such as sulfuric, trifluoroacetic, methanesulfonic acid or trifluoromethanesulfonic; or

b) nitric acid and a strong acid such as sulfuric, trifluoroacetic, methanesulfonic, trifluoromethanesulfonic or perchloric acid to give the corresponding 9-(acyl or sulfonyl amino)-7-nitro-8-demethyl-8-deoxytetracycline, 7.

#### SCHEME IV

In accordance with Scheme IV, a 9-(acyl or sulfonyl amino)-7-nitro-6-demethyl-6-deoxyletracycline, 7, is selectively N-alkylated with aldehydes or ketones in the presence of acid and hydrogen to the corresponding 7,9-di(substituted amino)-6-demethyl-6-deoxyletracycline, 8, by methodology known to those skilled in the art (U.S. Patents 3,226,436 and 3,518,306).

#### SCHEME V

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4 X = NR¹R²(R¹ = R² or R¹≠R²)

6 X = halogen

7 Y = NO2

 $\bar{8} X = NHR^3(R^3 = R^1 \text{ or } R^2)$ 

In accordance with Scheme V. Compounds 4,6,7 or 8 are selectively N-alkylated in the presence of tormaldehyde and either a primary amine such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or Dilysine, (L or Dilysine), (L or Dilysine) and the substituted congeners to give the corresponding Mannich base adduct, pyrrolidine, piperdine or their substituted congeners to give the corresponding Mannich base adduct, 9.10.11 or 12 or the desired intermediate or of the biologically active 7-(austituted)—Gleubituted amino)—6-demethyl-6-deoxytetracyclines. Contempleted equivalents include those substituted morpholine, pyronolidine or piperdine moieties wherein the substituents are chosen to provide the requisite increase in solubility without adversely affecting antibacterial activity.

The 7-(substituted)-9-(substituted amino)-8-demethyl-8-deoxyretracyclines may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, mamganese and complex salts; inorganic and or(Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). Preferably, the 7-(substituted)-9-(substituted amino)-8-demethyl-6-deoxyretracyclines are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroblodic, phosphoric, hiftic or sulfats; or organic salts such as acetate, benzoate, citrate, cysteiner or other amino acids, tumartae, glycotate, maleste, succinate, hardrate alkylacium or contact or any sulfatorate. In all cases, the salt formation occurs with the C(4)-dimethylamino group. The salts are preferred of or oral and peranteral administration.

#### BIOLOGICAL ACTIVITY

# Methods for in Vitro antibacterial evaluation (Tables I-V)

The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth of the test organism, is determined by the agar dilution method using 0.1 ml Muller-Hinton III agar (Baltimore Biological Laboratories) per well. An inoculum level of 1-5 x 10° CFU/ml, and a range of antibiotic

concentrations (32-0.004 µg/ml) is used. MIC is determined after the plates are incubated for 18 hours at 35°C in a forced air incubator. The test organisms comprise genetically defined strains that are sensitive to tetracycline and resistant strains that are insensitive to tetracycline, either by preventing the artitionic from interacting with bacterial ribosomes (tetM) or by a tetK encoded membrane protein which confers settarcycline resistance by energy-dependent efflux of the artibilities from the cell.

#### E. coli in Vitro Protein translation System (Table VI)

An in vitro, cell free, protein translation system using extracts from E. coli strain MRE 600 (tetracyclinesensitive) and a derivative of MRE 600 containing the tetM determinant has been developed based on literature methods. [J. M. Pratt, Coupled Transcription-translation in Prokaryotic Cell-free Systems, Transcription and Translation, a Practical Approach, (B. D. Hames and S.J. Higgins, eds.) p. 179-209, IRL Press, Oxford-Washinston. 18841.

The antibiotics are added to exponentially growing cultures of tetracycline-susceptible E. coll at growth inhibitory concentrations. After 30 minutes, excess antibiotic is removed from the bacteria by Contribugation and the organism is resuspended in fresh growth medium. The ability of bacteria to resume growth is monitored. Washing of inhibited cells alloviates growth inhibition due to chloretracycline, but not that caused by polymyxin. This reflects the different binding characteristics of the drugs. Chloretracycline binds reversibly to bacterial ribosomes, while polymyxin remains fightly associated with its target, the cytoplasmic membrane, and continues to prevent bacterial growth even when excess artibiotic is removed.

#### In Vivo Antibacterial Evaluation (Table VII)

The therapeutic effects of tetracyclines are determined against acute lethal infections with various staphylococcal and E. coil strains. Fernale mice, strain CD-1 (Charles River Laboratories), 20 ± 2 grams, are challenged by an intraperitoneal injection of sufficient bacteria (suspended in broth or hog mucin) to kill non-treated controls within 24-48 hours. Antibactorial agents, contained in 0.5 ml of 0.2% aqueous agar, are administered subcutaneously or orally 30 minutes after infection. When an oral dosing schedule is used, arimals are deprived of food for 5 hours before and 2 hours after infection. Five mice are treated at each 30 dose level. The 7 day survival ratios from 3 separate tests are pooled for calculation of median effective dose (EQs.).

#### E. coli in Vitro Protein Translation System(Table VIII)

An in vitro, cell free, protein translation system using extracts from E. coll strain MRE600 (tetracycline sensitive) and a derivative of MRE600 containing the tetM determinant has been developed based on literature methods [J. M. Part. Coupled Transcription-translation in Prokaryotic Cell-free Systems, Transcription and Translation, a Practical Approach, (B. D. Hames and S. J. Higgins, eds) p. 179-209, IRL Press, Oxford-Washington, 1884].

40 Using the systems described above, the novel letracycline compounds of the present invention are tested for their ability to inhibit protein synthesis in vitro. Briefly, each 10µl reaction contains S30 extract (a whole extract) made from either letracycline sensitive cells or an isogenic tetracycline resistant (letM) strain, low molecular weight components necessary for transcription and translation (i.e. ATP and GTP), a mix of 19 amino acids (i.o. methionine). NA Enplate (either pR8322 or pUC119), and 4s either DMSO (control) or the novel tetracycline compound to be tested ("Novel Tc") dissolved in DMSO.

The reactions are incubated for 20 minutes at 37°C. Timing is initiated with the addition of the S30 extract, the lase component to be added. After 30 minutes, 25 µl of the reaction is remobed and mixed with 0.5 ml of 1N NaOH to destroy RNA and tRNA. Two ml of 25% trichloroacetic acid is added and the mixture incubated at room temperature for 15 minutes. The trichloracetic acid precipitated material is collected on so Whatman GPIC filters and washed with a solution of 10% trichloracetic acid. The filters are dried and the retained radioactivity, representing incorporation of <sup>35</sup>S-methionine into polypeptides, is counted using standard flouid scinilitation methods.

The percent inhibition (P.I.) of protein synthesis is determined to be:

### Testing Results

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The claimed compounds exhibit antibacterial activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially, strains of E. coli, S. aureus and E. faecalis, so containing the tetM resistance determinants (Table I). Notable is 7-dimerbylaminoj-9-fromylaminoj-6-demethyl-8-deoxytetracycline, as shown in Tables I and IV, which has good in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 89-5, surueus UBMS 90-1 and 90-2, E. coli UBMS 89-1 and 90-4) and is equally as effective as minocycline against succeptible strains.

7-(Dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyletracycline demonstrates effective activity against minocycline susceptible strains including a variety of recently isolated bacteria from clinical sources (Table V). With the exception of some Proteus spp., 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyletracycline's activity is superior to that of minocycline against other isolates.

Protein synthesis, directed by cell-free extracts from the fetracycline susceptible strain MRE-800, are inhibited by tetracycline, minocycline and the 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxytetracycline of this invention (Table 8). Protein synthesis, directed by cell-free extracts from strain MRE 600 (tetM), is resistant to tetracycline and minocycline, since 50% inhibition of protein synthesis required addition of approximately 5-fold more ambitioic than in extracts prepared from strain MRE 600 (Table VI). However, in contrast, 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyrtetracycline effectively inhibited protein synthesis in extracts prepared from either MRE 600 or MRE 600 (tetM) (Table VI). The evidence presented indicates that 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyrtetracycline is an inhibitor of protein synthesis at the ribosome level. The ability of 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyrtetracycline to inhibit bacterial growth aimost containly reflects directed inhibitor of bacterial synthesis. If so, then it is expected, like other tetracyclines, to exhibit a bacteriostatic effect against 25 suscentible bacteria.

7-(Dimethylamino)-9-(formylamino)-6-domethyl-6-deoxyletracycline binds reversibly to its target (the ribosome) since bacterial growth resumed when the compound was removed from the cultures by washing of the organism. Therefore, the ability of 7-(dimethylamino)-9-(formylamino)-6-domethyl-6-deoxyletracycline inhibit bacterial growth appears to be a direct consequence of its ability to inhibit protein synthesis at the obscience level.

The enhanced activity (Table VII) of 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyletracycline against tetracycline susceptible and resistant organisms (totM) is also demonstrated in vivo in animals infected with S. aureus UBMS 90-1 and 90-2. The ED<sub>20</sub>'s (Table VII) obtained for 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyletracycline are lower than those of minocycline.

The improved efficacy of 7-(dimethylamino)-9-(formylamino)-6-demethyl-6-deoxyletracycline is demonstrated by the in vitro activity against isogenic strains into which the resistance determinants, such as tetM, were cloned (Tables I-VI); the inhibition of protein synthesis by tetM ribosomes (Table VI); and the in vivo activity against experimental infections caused by strains resistant to the tetracyclines, due to the presence of resistance determinants, such as tetM (Table VII).

As can be seen from Tables I-V, compounds of the invention may be used to prevent or control important veterinary diseases such as mastitis, diarrhea, urinary tract infections, skin infections, ear infections, wound infections and the like.

# LEGEND FOR COMPOUNDS

5	LI	TTER NAME
10	A	7-(Dimethylamino)-9-(formylamino)-6-demethyl-6-de- oxytetracycline
	В	9-(Acetylamino)-7-(dimethylamino)-6-demethyl-6-de- oxytetracycline
15	c	7-(Diethylamino)-9-(formylamino)-6-demethyl-6-de- oxytetracycline
20	D	7-(Diethylamino)-9-(formylamino)-6-demethyl-6-de- oxytetracycline disulfate
25	E	9-(Acetylamino)-7-(diethylamino)-6-demethyl-6-de- oxytetracycline disulfate
30	F	9-(Acetylamino)-7-(diethylamino)-6-demethyl-6-de- oxytetracycline
35	G	9-(Formylamino)-7-iodo-6-demethyl-6-deoxytetracyc- line sulfate
	Н	9-(Acetylamino)-7-iodo-6-demethyl-6-deoxytetracycline sulfate
40	I	7-(Dimethylamino)-9[(trifluoroacetyl)amino)-6-de- methyl-6-deoxytetracycline sulfate
45	J	7-(Dimethylamino)-9-[[(phenylmethoxy)acety1]-amino]-6-demethyl-6-deoxytetracycline
50	K	9-[[(Acetyloxy)acetyl]amino]-7-(dimethylamino)-6-demethyl-6-deoxytetracycline

	L	7-(Dimethylamino)-9-[(hydroxyacetyl)amino)-6-demethyl-6-deoxytetracycline
5	М	9-[(Aminoacetyl)amino]-7-(dimethylamino)-6-demeth- yl-6-deoxytetracycline mono(trifluoroacetate)
10	N	[7S-(7a,10aa)]-[[9-(Aminocarbony1)-7-(dimethy1-amino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny1]amino}-oxoacetic acid ethyl ester
15	0	7-(Dimethylamino)-6-demethyl-6-deoxytetracycline hydrochloride (minocycline hydrochloride)
20	P	9-(Benzoylamino)-7-(dimethylamino)-6-demethyl-6-dexytetracycline
25	Q	7-(Dimethylamino)-9-[(4-methoxybenzoyl)amino]-6-demethyl-6-deoxytetracycline
30	R	7-(Dimethylamino)-9-[(2-methylbenzoyl)amino)-6-demethyl-6-deoxytetracycline
-	s	7-(Dimethylamino)-9-[(2-fluorobenzoyl)amino]-6-demethyl-6-deoxytetracycline
35	T	7-(Dimethylamino)-9-[(pentafluorobenzoyl)amino)-6-demethyl-6-deoxytetracycline
40	Ū	7-(Dimethylamino)-9-[[3-(trifluoromethyl)benzoyl]-amino)-6-demethyl-6-deoxytetracycline
45	٧	7-(Dimethylamino)-9-[(4-nitrobenzoyl)amino]-6-demethyl-6-deoxytetracycline
	w	7-(Dimethylamino)-9-[{(4-dimethylamino)benzoyl}- amino}-6-demethyl-6-deoxytetracycline
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- X 9-[(4-Aminobenzoyl)amino]-7-(dimethylamino)-6-demethyl-6-deoxytetracycline sulfate
- Y 7-(Dimethylamino)-9-[(2-furanylcarbonyl)amino]-6demethyl-6-deoxytetracycline
- 7- (Dimethylamino)-9-[(2-thienylcarbonyl)amino]-6demethyl-6-deoxytetracycline
- 7-(Dimethylamino)-9-[((4-nitrophenyl)sulfonyl)amino)-6-demethyl-6-deoxytetracycline
- BB 7-(Dimethylamino)-9-[(3-nitrophenyl)sulfonyl]amino]-6-demethyl-6-deoxytetracycline
- CC 7-(Dimethylamino)-9-[(phenylsulfonyl)amino]-6-demethyl-6-deoxytetracycline
  - DD 7-(Dimethylamino)-9-[(2-thienylsulfonyl)amino]-6demethyl-6-deoxytetracycline
  - EE 9-[[(4-Chlorophenyl)sulfonyl]amino]-7-(dimethyl-amino)-6-demethyl-6-deoxytetracycline
- FF 7-(Dimethylamino)-9-[(methylsulfonyl)amino]-6-demethyl-6-deoxytetracycline
- 40 GG 9-[[(2-Acetylamino)-4-methyl-5-thiazolyl]sulfonyl]amino]-7-(dimethylamino)-6-demethyl-6-deoxytetracycline
- 46
  HH [7S-(7a,10aa)]-[9-(Aminocarbonyl)-4,7-bis(dimeth-ylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl)car50 bamic acid methyl ester

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II 7-(Dimethylamino)-9-[[(dimethylamino)acetyl]-

		amino]-6-demethyl-6-deoxytetracycline sulfate
5	TC	Tetracycline hydrochloride
	JJ	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
10		[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-
		12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
		2-naphthacenecarboxamide disulfate
15		
	KK	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
		[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-
20		12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-di-
		oxo-2-naphthacenecarboxamide dihydrochloride
	LL	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
25		[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-
		12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
		2-naphthacenecarboxamide
30		
	MM	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,
		4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahy-
35		droxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-
		2-naphthacenecarboxamide dihydrochloride
	NN	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,
40		7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octa-
		hydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naph-
		thacenyl]-4-morpholineacetamide dihydrochloride
45	00	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
		[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-
		octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
50		2-naphthacenecarboxamide dihydrochloride

- PP [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(butylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12aoctahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2naphthacenecarboxamide dihydrochloride
- QQ [4S-(4alpha, 12aalpha)]-9[((Cyclopropylamino) acetylamino]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,l2a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
  - RR [45-(4alpha,12aalpha)]-9-[[(Diethylamino)acetyl]amino]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo2-naphthacenecarboxamide dihydrochloride
- SS [75-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro
  1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyll-1-pyrrolidineacetamide dihydrochloride
- TT [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,
  4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)amino]acetyl]amino]-1,11dioxo-2-naphthacenecarboxamide dihydrochloride
  - UU [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbony1)-4,-7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny1)-1-piperidineacetamide dihydrochloride
- 45 VV [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,-7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1H-imidazole-1-acetamide dihydrochloride

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5	ww	[48-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydr- oxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-
•		naphthacenecarboxamide dihydrochloride
	xx	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
10		[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,
		5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,
		11-dioxo-2-naphthacenecarboxamide dihydrochloride
15	YY	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,
		4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydr-
		oxy-9-[[2-(methylamino)-1-oxopropyl]amino]-1,11-
20		dioxo-2-naphthacenecarboxamide dihydrochloride
	zz	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
		[[4-(dimethylamino)-1-oxobutyl]amino]-1,4,4a,5,
25		5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,
		11-dioxo-2-naphthacenecarboxamide dihydrochloride
30	AAA	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-
30		bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahy-
		dro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naph-
		thacenyl]-alpha-methyl-1-pyrrolidineacetamide di-
35		hydrochloride
	ввв	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-
		[[(hexylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-
40		octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
		naphthacenecarboxamide dihydrochloride
45		
	ccc	[4S-(4alpha,12aalpha)]-9-[[(Butylmethylamino)-
		acetyl]amino]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,
		6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
50		dioxo-2-naphthacenecarboxamide dihydrochloride

DDD [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-5 naphthacenecarboxamide dihydrochloride EEE [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4, 10 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethyl)amino]acetyl]amino1-2-naphthacenecarboxamide dihydrochloride 15 FFF [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-20 N-(1-pyrrolidinylmethyl)-2-naphthacenecarboxamide GGG [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(4-morpholinvlmethyl)-2-naphthacenecarboxamide 30 HHH [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11, 12a-octahydro-3, 10, 12, 12a-tetrahydroxy-1, 11-dioxo-35 N-(1-piperidinylmethyl)-2-naphthacenecarboxamide III [4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,-7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride 45 JJJ [4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-50 2-naphthacenecarboxamide hydrobromide

		( - ( Aminocarbonyi) -4,
		7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahy-
6		dro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphtha-
		cenyl]amino]-2-oxoethyl]glycine
10	LLL	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-
		bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahy-
		dro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphtha-
15		cenyl]-1-azetidineacetamide
	MMM	[4S-(4alpha,12aalpha)]-9-[[(Cyclobutylamino)acet-
		yl]amino]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,
20		12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
		2-naphthacenecarboxamide
25		
30		
35		
40		
45		
50		

ANTIBACTERIAL ACTIVITY OF 9-(ACYLAMINO)-7-(SUBSTITUTED)-4-DEMETHYL-4-DEOXYTETBACYCLINES

									Ü	(lm/a)		ŀ					
									COMP	DNIND							1
ORGANISM	1	4	4	4	4	4	þ	4	4	Н	4	4	B	z	þ	Ħ	4
F. sureus UBMS 88-5 (setM)	90.0	0.12	0.12	0.25		0.5	-	-	22		0.25	4	-	32	7	220	0.12
S. surrus UBMS 88-4 (Serultive)	0.015	80.08	0.03	0.12	97	979	<0.015	975	•	7	0.12	-	-	*	\$10.03	9,0	90.0
S. surnu UBMS 90-1 (setM)	90.0	Q	50	5.0	•	*	-	-	95	-	22	•	7	ž	-	-	025
5. aureus UBMS 90-2 (setM)	9.0	£	0.12	0.12	7	0.5	0.5	9	91	~	900	۲۰	0.5	Ħ	7	22	90.0
S. serces UBMS 90-3 (Sensitive)	50.015	ğ	0.03	90:0	6.5	0.12	0.03	0.12	-	S	900	-	9.5	-	50.015	900	900
Courses UBMS 88-7 (set.K)	7		973	~	•	~	91	9	91	7	32	ž	>35		90:0	95	-
i. surrus IVES 2943 (meth. esistent)	•	3	-	-	•	7	r,	g	Š	•	æ	ă	232	g	-	7	-
5. dureus IVES 1983 (meth.	•	ğ	-	•	2		Ħ	32 25 ¢	Ħ	•	g	ķ	ğ	<del>ğ</del>	-		-
S. eurous ATCC 29213 (Sersitive)	\$0.015	0.12	\$10.02	\$0.015	\$10.02	\$10.03	Ş	0.12	-	90:0	20.03	9.5	0.5	52	\$0.015	\$0.015	0.03
S. carrous South (Sensitive)	\$0.03	0.12	0.03	0.03	50	0.12	0.03	0.12		20	\$0.015	95	-	~	\$0.015	90	0.12
i. facmolyticus AVAH 88-3	0.03	ð	0.12	£	•	7	90.0	7	รู	-	6.5	2	-	•	0.03	สู	55
f. faccalls 12201	0.12	0.5	0.5	-	2		92	~	92	7	0.25	•	0.25	g	•	7	0.12
E. farcalis ATCC 29212	50.015	0.12	90'0	0.12	2	57	972	0.25	•	-	90'0	7	0.25	Ħ	0.5	0.25	0.03
E. coli UBMS 63-1 (ter8)	33	×128	9	ķ	ķ	ž	ž	¥21×	ž	>32	91	ž	7	ř	•	91	22
E. coli UBMS 88-2 (Sensitive)	g12	7	979	9	ž	33	-	×128	æ	>32	•	ŭ	7	ķ	9.5	ē	ę
E. call UBMS 89-1 (1ctM)	9.12	Š	-	£	32	•	-	128	25	>35	-	32	7	<del>2</del> 2	<b>9</b>	-	0.12
E. all UBMS 89-2 (Sessitive)	0.12	2	93	ş	52	æ	-	92	33	ķ	60	텻	*	¥	6.5	•	0.15
E. coli ATCC 25922	90'0	,	0.25	0.5	32		Š	91	۶	2	,	2	,	ţ	900		010

ANTIBACTERIAL ACTIVITY OF 9-(AROYLAMINO) AND 9-(HETEROYLAMINO)-7-(SUBSTITUTED)-6-DEMETHYL-6-DEOXYTETRACYCLINES TABLEII

						MIC (ug/ml)	(lm/an		-			1
	-					COM	COMPOUND	-				1
ORGANISM	٩	9	4	S	4	7	>	×	×	H	7	d
S. Awrens UBMS 88-5 (terA)	-	60	4	7	•	-	7	35	80	16	80	7
S. surces UBMS 88-4 (Sensitive)	+	•	7	7	+	97	7	60	-	4	80	20.05
S. eureas UBMS 90-1 (111Af)	4	•		-	•	-	7	91	91	33	-	•
S. aureus UBMS 90-2 (111M)	-		7	-	7		-	<b>s</b> o	80	96	-	7
S. suress UBMS 90-3 (Sensitive)	-	•	-	-	7	0.5	0.5	€0	-	7	7	50.015
S. swred UBMS 88-7 (tets)	80	91	4	60	•	-	•	9	80	>35	33	90'0
S. eurose IVES 2543 (meth. resistant)	91	80	4	80	•	-	-	80	Ř	×32	33	-
S. eureus IVES 1983 (meth. resistant)	•	91	60	-	•	-	60	80	Ŕ	>32	35	-
S. surrus ATCC 29213 (Sensitive)	0.25	-	0.12	0.5		97	570	7	6,5	0.5	0.5	\$10.02
S. eurosa Smith (Sensitive)	-	•		-	-		0.5	•	-	7	7	50,015
S. Asemplyticus AVAH 88-3	-	8	80	•	+	-	•	91	•	>32		0.00
E. fuccelie 12201	•	60	8	•	-		•	91	35	32		+
E. fescalis ATCC 29212	-	80	7	-	-	-	•	80	•	80		9.5
E. coll UBMS 88-1 (1418)	×32	>32	7	23	>32	ž	>32	ž	Ř	>32	232	æ
E. coli UBMS 88-2 (Sensitive)	ž	×32	×32	>32	>35	>35	>35	, 33	Ķ	>32	š	9.5
E. coli UBMS 89-1 tretAn	ž	ž	Ñ	Š	Q.	>35	×32	8	ž	>32	ķ	91
E. colf UBMS 89-2 (Sensitive)	×32	232	ά×	>37	>32	232	>32	ž	š	>32	ž	0.5
E. rali ATCC 25922	ž	32	×32	>32	>35	232	>35	25	ž	>32	×32	0.25

TABLEIL

ANTIBACTERIAL ACTIVITY OF 9-(SULFONYLAMINO)-7-(SUBSTITUTED)-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (ug/ml)

				COMPOUNT	DVID			
ORGANISM	AA	Ħ	넉	DD	出	버	99	c
S. aureus UBMS 88-5 (tetM)	0.12	S	4	9.5	0.12	0.25	16	**
S. aureus UBMS 88-4 (Sensitive)	0.12	-	0.03	0.5	0.12	0.25	7	0.03
S. aureus UBMS 90-1 (telM)	0.5	61	4	<b>,</b>	0.25	0.25	33	c1
S. aureus UBMS 90-2 (tetM)	0.12	0.5	90.0	0.25	0.12	90.0	**	r4
S. aureus UBMS 90-3 (Sensitive)	90.0	0.12	4	0.25	0.12	0.12	2	≤0.015
S. aureus UBMS 88-7 (tet.K)	61	4	4	7	-	80	35	0.06
S. aureus IVES 2943 (meth. resistant)	+	4	4	4	0.5	91	>35	CI
S. aureus IVES 1983 (meth. resistant)	œ	œ	4	4	-	16	당	<b></b>
S. aureus ATCC 29213 (Sensitive)	0.12	90.0	≤0.015	0.03	0.03	0.03	0.5	≤0.015
S. aureus Smith (Sensitive)	0.12	0.25	4	0.03	0.12	0.12	t.)	≤0.015
5. luemolyticus AVAH 88-3	71	4	4	7	Š	Ω	Q	90:0
E. faecalis 12201	Ω	Ω	Q	Ω	Ω	Q.	δ	90
E. faecalis ATCC 29212	0.12	0.12	90:0	0.25	90:0	90.0	-	0.5
E. coli UBMS 88-1 (tetB)	16	>32	91	32	>32	œ	>32	91
E. coli UBMS 88-2 (Sensitive)	89	4	80	80	>37	۲1	>35	0.5
E. coli UBMS 89-1 (tetM)	7	Ω	Ω	ΩN	Ω	Ω	32	16
E. coli UBMS 89-2 (Sensitive)	16	16	16	16	>32	7	>32	0.5
E. coli ATCC 25922	4	7	61	4	>32	7	>32	0.5

		ᆲ	5.0	0.5	=	9.5	-	0.5	0.25	0.5	0.25	0.12	0.25	0.5	0.25	0.25	0.25	~	0.5	92	0.12	0.25	0.5	~	0.5	0.25	٥.	~ ′	, ;	, ,	, 0	0.25	0.12	0.12				
5		a	-	-	F.	-	2	2	-	-	-	0.12	6.6	-	-	-	6.0	<b>e</b> a	2	91	0.5	-	-	•	-	5.0	5.0	en e		· •		-	0.25	0.25				
10	1111160)-	릙	>32	>32	*	>32	>32	>32	3.2	> 3.2	> 3.2	6.9	COM1	> 32	> 3.2	, 32	32	×32	32	×32	0.5	2	•	32	•	~	~	>35	3			3.2	2	2				
15	TABLE (A RHIBACTERIAL ACIIVIITO PO-CENTRADO-7-CSUBSTITITED)- A. Orbethel A. Pervytrabote infe	şi	-	-	N	-	16	80	-	-	-	0.25	CO#1	-	-	-	0.05	91	80	2	0.5	0.5	0.5	16	-	0.5	9.0	32	3 .	5.0	-	-	0.25	0.25				
20	TABLE (A ACTIVITY OF 9. (ACYLANINO)-7-(S)	1	0.25	9.12	E E	0.25	-	0.5	0.12	0.12	0.12	9	0.25	0.12	0.12	0.12	90.0	2	0.25	4	20.015	90.0	0.12	0.5	0.12	90.0	0.12		- 3		90.0	0.12	90.0	90.0		ated	5	
25	TIVITI OF	최	0.25	0.12	-	0.25	-	-	0.12	0.25	0.25	0.03	0.25	0.25	0.25	0.25	9.12	2	0.25	,	90.0	0.12	0.25	0.25	0.25	0.03	0.15			9	40.015	0.12	0.12	90.0		- Contaminated	. Not Tested	
	CTERIAL AC	, 3	0.25	0.25	¥	0.25	2	-	0.25	0.25	0.25	0.03	0.25	0.25	0.25	0.25	0.12	4	0.5	•	90.0	0.25	0.25	-	0.25	0.12	0.25	N f	;	;	0.03	0.25	0.12	0.12	2	CONT	*	
30	× ×			ens.	sens.				***	et Sens.			***					8733	87210	27853	7-69/		Teth	Tetk	1018		10.1				•	H 88-3		212				
35			UBMS 88-1 Tet8	J3272 let sens.	MC4100 Tet sens.	MC4100 TetB	PRP1 TetA	J3272 TetC	UBMS 89-1 TetM	calf UBHS 89.2 Tet Sens.	J2175	BAJ9003	UBMS 90-4 TetM	coli UBMS 90-5	#311 (NP)	ATCC 25922	coli 33272 TetD	meriescens FPOR 8753	maltophilia NEMC 87210	Ps. scruginosa ATCC 27853	aureus NEMC 8769/89-4	Bureus UBMS 88-4	aureus USMS 88-5 TetM	sureus USHS 88-7 TetK				1VES 2943		TAN TANK TOWN	BUFBUR ATCC 29213	S. hemolyticus AVRAN 88-3	Enterococcus 12201	faccalia ATCC 29212				
40			E. coli u	100		E. coli H	E. coli P	E. coll .	E. cott u	E. cott u		E. coli B	001	E. coli U		0011	E. colf J	S. series	X. meltop	Ps. serug		S. sureus						S. aureus				S. henoly	Enterocod	E. faccal				
45																																						
50																																						

5		긻	0.25	0.25	=	0.25	-	0.25	0.25	0.25	0.25	90.0	0.25	0.25	0.25	0.25	0.12	2	0.5	80	90.0	0.25	0.25	-	0.12	0.12	0.25	2	2	0.12	2	0.25	0.25	0.12	0.25
		3	*32	*32	*	× 32	>32	× 32	×32	> 32	*32	-	> 32	>32	×32	×32	> 32	>32	>32	×32	4	10	32	32	32	4	16	>32	>32	4	>32	60	>35	•	J
10	1111160).	의	0.5	0.5	7	6.9	-	0.5	0.12	0.5	0.5	90.0	0.5	0.5	0.25	0.25	0.25	4	0.12	32	90.0	0.25	0.25	0.25	0.25	0.12	0.12	0.25	0.5	0.12	6.0	0.12	0.12	0.12	0.06
15	O)-7-(SUBS	Ħ	6.9	0.5	-	0.5	2	0.5	0.25	6.5	0.5	90.0	0.5	0.5	0.5	0.5	0.12	,	0.5	16	0.03	0.25	0.25	2	0.25	0.12	0.25	2	2	0.12	2	0.25	0.5	0.25	0.25
20	FABLE 1A (CONT) ACTIVITY OF 9-(ACYLAMINO)-7-(S) 5-DEMETHYL-6-DEGXYTETRACYCLINES	SS	0.25	0.25	Ė	0.25	6.9	0.25	0.12	0.25	0.25	40.015	0.25	0.25	0.12	0.25	0.12	2	6.0	16	0.03	0.12	0.25	6.5	0.12	0.12	0.12	-	-	0.12	0.5	0.12	0.25	0.12	0.12
25	TABLE I IVITY OF 9-	8	-	-	*	-	2	-	0.25	-	-	90.0	0.5	-	0.5	0.5	0.25	•	0.25	32	90.0	0.25	0.25	0.5	0.25	0.25	0.25	-	-	0.25	0.25	0.12	0.5	0.12	0.12
30	TABLE IA (CONT) ANTIBACTERIAL ACTIVITY OF 9-(ACYLAMINO)-7-(SUBSTITITED)- 6-DEMETNYL-6-DEDXYTETRACTELINES	밁	4	2	7	2	32	•	-	2	~	0.25	~	2	2	2	2	>32	2	>32	0.12	0.5	0.5	•	0.5	0.5	0.5	9	16	0.25	60	0.5	2	6.5	0.25
35	ANTIBA		1 Tet8	t sens.	et sens.	818	_	2	1 TetM	UBHS 89-2 Tet Sens.			f Teth		•	22	2	DR 8733	EMC 87210	TCC 27853	7-68/69	7-9	UBNS 88-5 Teth	UBMS 88-7 TetK	UBMS 90-1 TetM	0.3	UBMS 90.2 TetM	573	î	(44)	983	9213	VHAH 88-3	-	29212
40									coli UBHS 89-1 Teth	coli UBHS 89-2	coli J2175	coli BAJ9003	coll UBMS 90-4 Teth	COLI UBMS 90-5	CO(( #311 (MP)	coli ATCC 25922	coll J3272 TetD	mariescena FPOR 8733	maitophilla NENC 87210	Ps. acruginosa ATCC 27853	aureus NENC 8769/89-4	4-88 SHBD snaine	eureus UBNS 82	eureus UBHS 80	BUT BUT UBHS 90	aureus UBMS 90-3	aureus USMS 9(	eureus IVES 2943	aureus ROSE (MP)	BUTCUS SHITH (MP)	aureus IVES 1983	S. aureus ATCC 29213	S. hemolyticus AVHAH BB-3	Enterococcus 12201	E. faecalls ATCC 29212
45			E. co	<b>E</b> . co	E. Co	E. co	E. CO	E. co	E. co	E. C0	E. co	F. 0	E. CO	f. co	E. C.	E. 00	F. co	S. m.	×	Ps.	2.	. s	. · · ·	. s		S. 8.	. s	2. e.	. s	S	. s	S. B.	S. he	Enter	£. ?
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		000	0.5	×	0.12	0.5	-	0.5	0.25	0.5	0.5	0.12	0.5	0.5	0.5	0.5	0.25	•	0.5	32	0.25	0.5	0.5	~	-	0.5	0.5	4	4	0.25	,	-	0.5	0.25	0.25
5		333	-	L	0.25	2	2	-	0.25	2	2	0.12	-	2	-	-	0.5	16	0.25	, 32	0.12	0.5	0.5	-	-	0.25	0.25	-	2	0.5	-	0.5	0.5	0.25	0.12
10	TTTED).	88	0.5	1.7	0.25	0.5	0.5	0.5	0.25	0.25	0.25	90.0	0.25	0.25	0.5	0.12	0.12	4	4	91	90.0	0.25	0.5	2	0.25	90.0	0.25	•	16	0.12	4	0.25	0.5	0.25	0.12
15	O-7-(SUBST	VVV	0.5	F. 8	0.12	0.5	0.5	0.5	0.12	0.5	0.5	90.0	0.5	5.0	0.25	0.25	0.12	•	0.5	*32	0.12	0.25	0.25	0.5	0.5	0.25	0.25	0.5	2	0.25	0.5	0.25	0.5	0.12	0.12
20	TABLE IA (CONT) Y OF 9 (ACYLAMINO YL-6-DEOXYTETRACY	77	*32	1.11	2	>32	*32	32	32	9,	16	-	16	9.	91	••	•	*32	32	> 32	-	7	•	91	80	2	•	×32	*32	2	×32	2		10	•
25	TABLE IA (CONT) ACTIVITY OF 9 · (ACYLAMIMO) - 7 · (SI 6 · DEMETHYL - 6 · DEOXYTETRACYCLINES	ដ	0.5	0.5	-	0.5	2	-	6.0	0.5	6.0	90.0	0.5	6.0	0.5	o. s	0.25	•	•	16	0.12	0.5	0.5	,	0.25	0.12	0.25	80	80	0.25	7	0.5	5.0	0.25	0.12
30	TABLE IA (CONT) ANTIBACTERIAL ACTIVITY OF 9 · (ACYLANINO) - 7 · (SUBSTITITED) · 6 · DEMETATL - 6 · DECXYTETRACYCLINES	×	0.5	0.5	¥	-	-	-	0.12	0.5	0.5	90.0	0.5	0.5	0.5	0.5	0.25	4	0.5	3.2	0.12	0.25	0.25	-	0.25	0.25	0.25	-	-	0.25	-	0.25	0.5	0.12	0.12
35	ANTIBAC		1 Tet8	78.	et sens.	618		÷	1 TetM	UBMS 89-2 Tet Sens.			4 TetM	•	•	22	40	08 8733	EMC 87210	TCC 27853	7-68/69-4	9.4	UBMS 88-5 TetM	8-7 TetK	0-1 TetM	0.3	UBHS 90-2 TetM	943	HP)	(HP)	983	9213	VHAH 88-3	0.1	29212
40			colf USMS 88-1 Tet8	coli J3272 sens.	coli MC4100 Tet sens	soli MC4100 Tet8	coli PRP1 TetA	coli J3272 Tetc	coli UBMS 89-1 TetM	coli UBMS 89-	coli J2175	coli BAJ9003	coli UBMS 90-4 Teth	coli UBMS 90-5	coli #311 (MP)	coli ATCC 25922	coli J3272 Tetô	mariescens FPOR 8733	maitophilia NEMC 87210	s. acruginosa ATCC 27853	5. aureus NEHC 8769/89-4	aureus UBMS 88-4	aureus usas a	aureus UBNS 88-7	aureus dams 90-1	Ecreus UBMS 90-3	eureus usas 9	aureus IVES 2943	aureus ROSE (MP)	Bureus SHITH (MP)	S. aureus 1vES 1983	aureus ATCC 29213	5. hemolyticus AVHAH 88-3	Enterococcus 12201	E. faecalls ATCC 29212
45			. G	F. C.	. o.	£. 00		E. C.	۴. د	E. C.	E. C.		E. C.	£. cc	£. 00	f. c.	£. cc	ě.	×. #	4	. s	S	.s		S. 8	S	· · ·	S	. s	. s	S	. s	S. he	Ente	
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5	TABLE IA (CONT) ANTIBACÍERIAL ACTIVITY OF 9-(ACYLANINO)-7-(SUBSTITITED)- 6-DEMETHYL-6-DEOXTTETRACYCLINES	1	* 32	91	-	> 32	> 3.2	>32	•	3.2	3.2	0.25	:	91	•	16	3.2	×32	•	> 3.2	0.12	0.5	-	2	-	0.5	0.5	4	•	0.5	•	0.5	2	-	0.5
10	NO)-7-(SUB CYCLINES	X X	0.25	T.N.	0.12	0.25	2	0.5	0.25	0.25	0.25	0.03	0.25	0.25	0.25	0.25	0.12	4	0.5	•	0.25	0.25	0.25	0.5	0.25	21.0	0.12	~	~	0.12	~	0.25	0.5	0.12	90.0
15	TABLE IA (CONT) Y OF 9-(ACYLAMI IYL-6-DEOXTTETRA	999	0.25	T.#	90.0	0.25	-	-	0.12	0.25	0.25	0.03	0.25	0.25	0.25	0.12	0.12	J	6.0	80	0.25	0.12	0.12	-	0.25	0.12	0.12	2	2	0.12	~	0.25	0.5	0.12	90.0
15	TABLE IA (CONT) ACTIVITY OF 9-(ACYLANINO)-7-(SI 6-DEMETHYL-6-DEOXTIETRACYCLINES	1	0.25	¥	90.0	0.25	2	-	0.12	0.25	0.25	20.015	0.12	0.25	0.25	0.12	0.12	•	0.25	80	0.25	0.12	0.12	-	0.12	0.12	0.12	2	8	0.12	2	0.12	0.25	0.12	90.0
20	ERIAL ACT 6-DE	3	2	¥.	0.5	J	4	~	0.5	4	4	0.25	6.9	0.5	0.5	5.0	0.5	7	-	32	0.12	0.25	0.5	2	0.5	0.25	0.25	2	80	0.25	2	0.5	2	0.25	0.25
25	ANTIBACT				,					ens.									10	53	,			×											
30			USMS 88-1 TetB	J3272 sens.	MC4100 Tet sens	MC4100 Tet8	PRP1 TetA	J3272 TetC	JBMS 89-1 TetM	UBMS 89-2 Tet Sens.	J2175	8AJ9003	UBMS 90-4 TetM	UBMS 90.5	#311 (MP)	ATCC 25922	J3272 Tetb	mariescens fPOR 8733	maltophilia NEHC 87210	acruginosa ATCC 27853		7-88 SM80	UBMS 88-5 1	UBHS 88-7		UBMS 90-3	UBMS 90-2 TetM			SMITH (MP)	eureus 1VES 1983	aureus ATCC 29213	hemolyticus AVHAH 88-3	Enterococcus 12201	E. faecalis ATCC 29212
35			E. colf u	E. coti	E. colf #	E. coli #	E. coli P	E. colf 5	E. colt U	E. colf U		E. colf 8					E. coli J	S. maries	X. maltop	Ps. acrus	S. sureus	S. aureus	S. BUTeus	S. sureus	S. sureus	S. aureus	S. sureus	S. sureus	S. sureus	S. sureus	S. aureus	S. sureus	S. hemoly	Enterococ	E. faecal
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45																																			
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5	TABLE (A (CONT) ANTIBACIERIAL ACTIVITY OF 9-(ACTLANINO)-7-(SUBSTITITED)- 6-DEMETHTL-6-DEOXYTETRACTCLINES																																		
10	0)-7-(SU 7CLINES	×	0.5	90.0	=	0.25	4	0.5	0.25	0.5	0.25	0.03	0.25	0.5	0.25	0.25	0.12	•	0.5	32	0.5	0.25	0.25	,	0.5	0.12	0.25	7		0.25	•	0.25	0.24	0.24	0.25
	TABLE IA (CONT) T OF 9-(ACYLAMIN YL-6-DEOXYTETRAC	딐	6.5	0.25	×	6.0	-	0.5	0.25	0.5	0.25	90.0	0.25	0.25	0.25	0.25	0.12	~	-	•	0.12	0.25	0.25	2	0.25	0.12	0.25	~	2	0.25	2	0.25	0.25	0.25	0.25
15	TABLE IA (CONT) ACTIVITY OF 9 · (ACYLAMINO) - 7 · (S) 6-DEMETHYL - 6 - DEOXYTETRACYCLIMES	KKK	, 32	> 32	32	.32	> 32	.32	> 32	,32	> 32	91	, 32	> 32	*32	× 32	×32	× 32	> 32	* 32	32	32	> 3.2	>32	>32	91	32	* 32	>32	91	>32	32	*32	>32	91
20	181AL ACTI 6-DEM	777	>32	*32	-	*32	*32	*32	3.2	*32	*32	•	×32	*32	>32	>32	>32	>32	91	>32	•	•	60	16	91	2	•	32	*32	•	3.2	•	16	16	9.
25	ANTIBACTE																		10	53				_									.3		
30			UBMS 88-1 Tet8	J3272 sens.	MC4100 Tet sens.	MC4100 Tet8	PRP1 TetA	J3272 TetC	UBMS 89-1 TetM	UBMS 89-2 Tet Sens.	J2175	8AJ9003	UBMS 90-4 TetM	UBMS 90.5	coll #311 (#P)	ATCC 25922	J3272 TetD	Beriescens FPOR 8733	maitophilia NEMC 87210	acruginosa ATCC 27853	NEMC 8769/89-4		SMBO	UBMS 88-7		UBHS	UBMS 90-2 TetM			SHITH (MP)	aureus IVES 1983	AUFRUE ATCC 29213	hemolyticus AVNAH 88-3	12201	E. faccalis ATCC 29212
35			E. coli UB			coli			E. coll UB		E. coli 32	E. coli 9A	E. coti us	E. coll un	E. coll #3		E. coli 13	S. merieso	X. mettoph	Ps. scrugi	S. BUTCELS NEMC	S. sureus	S. sureus	S. sureus	S. aureus	S. BUTEUS	S. BUTEUR	S. hemolyt	Enterococcus 12201	E. faccall					
40																																			
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TABLE IV

Susc ptibility of Sensitiv and Resi	stant (tetM) O	rganisms to 1	Tetracyclines
Organisms		MIC(μg/ml)	
	Α	0	TC
E. coli UBMS 88-2 (Sensitive)	0.12	0.5	ND
E. coli UBMS 90-4 (tetM)	1	64	64
S. aureus UBMS 88-4 (Sensitive)	<0.015	0.03	0.12
S. aureus UBMS 88-5 (tetM)	0.03	2	32
S. aureus UBMS 90-3 (Sensitive)	< 0.015	0.03	0.12
S. aureus UBMS 90-1 (tetM)	0.12	4	32
N. gonorrhoeae IL 611 (Sensitive)	0.06	0.5	ND
N. gonorrhoeae 6418 (tetM)	1	>32	>32
E. faecalis UBMS 90-6 (tetM)	0.12	8	32
E. faecalis UBMS 90-7 (tetM)	0.5	8	32

TABLE V

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# In vitro Activity of Compounds A and O Against Clinical Isolates

				IIC (us/ml)+	
Organism	No. Tested	Antibiotic	Range	MICso	MIC90
Neisseria	(9)	Α	0.015 - 1.00	0.03	1.00
gonorrnoeae		О	0.03 - >32.00	0.25	>32.00
Haemophilus	(18)	Α	<0.008 - 0.06	0.06	0.06
influenzae		О	0.06 - 0.25	0.12	0.25
Enterococcus	(14)	Α	<0.015 - 2.00	0.12	1.00
Jaecaus		О	<0.015 - 16.00	4.00	16.00
Enterococcus	(11)	Α	<0.015 - 2.00	0.06	2.00
faecium		0	<0.015 - 16.00	8.00	16.00
Escherichia coli	(10)	Α	0.06 - >32.00	0.25	>32.00
		0	0.12 - 32.00	0.25	16.00
Klebsiella	(10)	Α	0.25 - >32.00	0.50	0.50
рпештопіае		0	1.00 - >32.00	1.00	4.00
Proteus spp.	(9)	Α	0.50 - >32.00	2.00	>32.00
indole +		0	1.00 - >32.00	16.00	>32.00
Bacteroides spp.	(15)	A	<0.15 - 4.00	0.25	2.00
		0	<0.15 - 16.00	1.00	4.00
	Neisseria * gonorrhoeae Haemophilunae Influentae Enterococcus faecalis Enterococcus faecium Escherichia coli Klebsiella pneumoniae Proteus spp. indole +	Neisseria   (9)	Neisseria   (9)	Organism         No. Tested         Antibiotic         Range           Neisseria gonorhoeae         (9)         A         0.015 - 1.00           1 gonorhoeae         0         0.03 - >32.00           Haemophilus influenzae         (18)         A         <0.008 - 0.05	Neisseria   (9)

<sup>+</sup> MIC<sub>50</sub> = minimum concentration required to inhibit 50% of strains tested. MIC<sub>90</sub> = minimum concentration required to inhibit 90% of strains tested

# TABLE V (CONT) In Vitro Activity of KK and Comparative

# Antibiotics vs Recent Clinical and Agricultural Isolates

5				HIC (μg/ml)	
	Organism	[No. Tested]	<u>K.K.</u>	<u>o</u>	T.C.
10	Staphylococcus aureus, methicillin-resistant	£153	0.12-2	0.06-4	0.25->64
	Staphylococcus aureus, methicillin-susceptible	[15]	0.12-0.25	0.03-0.12	0.12-1
15	Staphylococcus Coagulase-negative, methicillin-susceptible	(16)	0.12-8	0.03-1	0.12.>64
	Enterococcus faecalis	[10]	0.015-0.12	0.03-16	0.12-64
20	Enterococcus faecium	[10]	0.03-0.12	0.03-16	0.12-64
	Enterococcus spp. Vencomycin-resistant	[8]	0.015-0.06	0.03-16	0.12->64
25	Streptococcus pyogenes	[10]	0.06-0.12	0.03-2	0.12-16
	Streptococcus agalactiae	[10]	0.06-0.25	0.12-16	0.25-64
	Streptococcus pneumoniae	[10]	0.03-0.25	0.06-0.5	0.12-2
30	Listeria monocytogenes	(8)	0.06-0.12	0.015-0.03	0.12-0.5
	Escherichia coli (Clinical)	[30]	0.12-4	0.25-32	0.5->64
35	Escherichia coli (Agricultural)	(15)	0.12-4	1-16	2->64
	Shigelle spp.	[14]	0.06-0.5	0.25-8	0.25->64
	Klebsiella pneumonise	. [10]	0.25-8	0.5-8	0.5->64
40	Klebsiella oxytoca	[10]	0.5-1	0.5-4	0.5-1
	Citrobacter freundii	[10]	0.25-8	0.03-32	0.5-16
	Citrobacter diversus	[10]	0.25-1	0.25-4	0.5-4
45	Salmonells spp. (Clinical)	(11)	0.25-0.5	0.5-16	0.5->64

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# TABLE V (CONT) In Vitro Activity of KK and Comparative Antibiotics vs Recent Clinical and Agricultural Isolates

5				MIC (μg/ml)	
	Organism	[No. Tested)	<u>KK</u>	<u>o</u>	<u>1 C</u>
10	Salmonella cholerasuis (Agricultural)	(15)	0.5-16	2->64	1.>64
	Serratia mercescens	(10)	2 - 8	1 - 8	8->64
	Enterobacter cloacae	[10]	0.5-1	0.25-4	0.5-2
15	Enterobacter aerogenes	[10]	0.5-1	0.5-1	0.5-1
	Providencia spp.	(13)	2 - 8	4->64	1->64
	Proteus mirabilis	[26]	1 - 32	1-32	0.5-64
20	Proteus vulgaris	(18)	0.5-4	0.5-16	0.25-64
	Horganella morganii	(16)	0.5-4	0.25-32	0.25->64
25	Pseudomonas aeruginosa	. [10]	1-16	1-16	2 - 32
25	Xanthomonas maltophilia	(10)	0.5-2	0.12-1	8-16
	Moraxella catarrhalis	[18]	0.06-0.12	0.03-0.12	0.06-0.5
30	Neisseria gonorrhoeae	(14)	0.25-1	0.5-64	1->64
	Haemophilus influenzae	(15)	0.5-2	0.5-2	1-32
35	Pasturella multocida (Agricultural & Clinical)	[17]	0.03-0.25	0.015-4	0.06-16
35	Bordetella bronchiseptica (Agricultural)	[10]	0.12	0.06-0.12	0.12-0.25
	Bacteroides fragilis	(11)	0.06-0.2	<0.008-16	0.25.>64
40	Bacteroides fragilis group	[10]	0.06-2	<0.008-4	0.25-32
	Bacteroides spp.	[9]	0.03-1	0.03-16	0.25->64
	Clostridium difficile	[12]	0.03	0.015-16	0.12-32
45	Clostridium perfringens	(16)	0.03-1	<0.008-16	0.015-16
	Clostridium spp.	[9]	0.015-0.12	<0.008-16	0.015-64
50	Anserobic Gram (+) Cocci	(15)	0.015-0.06	0.05-8	4->64

TABLE VI

Antibiotic	ICso(µg	ml) *
	TC Sensitive Host	Tet M Host
Tetracycline	0.6	2.0
Compound O	0.4	2.0
Compound A	<0.3	0.4

<sup>\*</sup>Concentration of antibiotic required to inhibit protein synthesis by 50% compared to a drug-free control

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TABLE VII

# In vivo Protective Activity of Compounds A and O in Mice Infected with Staphylococci Containing the tetM Determinant

Organism	Compound	ED <sub>50</sub> (mg/kg)
S. aureus UBMS 90-1	Α	0.22
	О	1.7
S. aureus UBMS 90-2	Α	0.49
	0	3.0

<sup>&</sup>lt;sup>+</sup> Median effective dose protecting 50% of the infected mice, single subcutaneous dosing.

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TARLE VIII

	In Vitro Transcription a	nd Protein Translation S n	sitivity to Tetracyc	line Comp unds
5	COM	POUND	% INH	IBITION
	Organism	Concentration	Wild Type S30	TetM S30
	KK	1.0 mg/ml	92	95
	1	0.5 mg/ml	90	96
0	1	0.25 mg/ml	89	93
	1	0.12 mg/ml	84	93
		0.06 mg/ml	82	89
		0.03 mg/ml	81	75
5	MM	1.0 mg/ml	99	99
3	1	0.2 mg/ml	98	97
		0.06 mg/ml	95	92
	00	1.0 mg/ml	99	99
	}	0.2 mg/ml	97	95
0		0.06 mg/ml	94	87
	QQ	1.0 mg/ml	99	99
	ł	0.2 mg/ml	97	95
		0.06 mg/ml	92	85
5	RR	1.0 mg/ml	99	99
	1	0.2 mg/ml	97	97
		0.06 mg/ml	93	90
	W	1.0 mg/ml	99	98
0	l	0.2 mg/ml	93	92
		0.06 mg/ml	91	79
	ww	1.0 mg/ml	99	98
		0.2 mg/ml	99	97
		0.06 mg/ml	93	88
5	xx	1.0 mg/ml	98	97
	į	0.2 mg/ml	96	89
		0.06 mg/ml	85	78
	Minocycline	1.0 mg/ml	98	68
)	1	0.2 mg/ml	89	43
		0.06 mg/ml	78	0

When the compounds are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, Gilluents and the like, and may be administered orally in such forms as tablets, capaules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 0.05 to 5% of suspensions containing, for example, from about 2.0 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

An effective amount of compound from 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intravenous, intravenous), intravenous, interavenous, inte

compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline collulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmacoutical compositions may be advantageously included, such as flavoring agents, coloring agents, such anticivalents, for example, vitamin E, accorbic acid, BHT and BHA.

The proferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is proferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be repeared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or disporsions and sterile powders for the extemporaneous preparation of sterile injectable solutions or disporsions. In all as cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The invention will be more fully described in conjunction with the following specific examples which are not to be construed as limiting the scope of the invention.

#### Example 1

 [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11dioxo-2-naphthacenecarboxamide sulfate (1:1)

To a stirred (see bath cooled solution of 0.444 g of [4S-(4-1,2as)]-4,7-bis(dimethylamino)1,44,6,5,6,6,6,1,1,2a-ocathylor-3,10,12,12-6,ertanyloroy-1,1-dioso-2-napthicaene-carboxamide hydrochiosside, prepared by the procedure described in U.S. Patent 3,226,436, dissolved in 15 ml of sulfuric acid is added 0.101 g of sodium nitrate. The mixture is stirred in the cold for 45 minutes followed by the dropwise addition to 500 ml of diethyl either. The resulting solid is collected, washed with diethyl either and dried to give 0.6 g of the desired product as a solid.

MSIFAB; mz 503(M+1) and 601(M+H,SO<sub>4</sub>+H).

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Example 2

[4S-(4a,12aa)]-9-Amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1)

A mixture of 2.0 g of product from Example 1 in 20 ml of 2-methoxyethanol is stirred for 10 minutes and filtered. The filtrate is shaken, in a pressure bottle, with 1.0 g of 10% palladium-on-carbon and 5 ml of 2N sulfuric acid, under 30 lbs. of hydrogen pressure, for 1 hour. The reaction mixture is filtred and the filtrate concentrated in vacuo to half volume. The solution is poured into 100 ml of diethyl ether, the solid occleted, washed with diethyl other and dried to give 1.6 g of the desired product as a solid. MS(FAB) m2 473(M + H).

# Example 3

[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

To a stfrring 0°C solution of 3.0 g of product from Example 2, 0.451 g of anhydrous sodium acetate and 50 ml of 98% formic acid is added, dropwise, 7.4 ml of acetic anhydride. The reaction is stirred at 0°C for 10 minutes followed by stfrring at room temperature for 1 hour. The mixture is poured into 500 ml of deithyl either and the precipitate collected. The solid is washed with diethyl either and dried to give 2.9 g of the desired product.

MS(FAB): m/z 501 (M+H).

#### Example 4

15 [4S-(4α,12aα)]-4,7-Bis(dimethy)lamino)-9-(formy)lamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

To a solution of 3.5 g of product from Example 3 in 150 ml of distilled water is added sufficient 0.75N suffuric acid to bring the reaction solution of pH 3.6. The solution is lyophilized to give 3.6 g of the desired a salt.

MS(FAB); m/z 501 (M+H).

#### Example 5

25 [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride

To a solution of 3.5 g of product from Example 3 in 150 ml of distilled water is added sufficient 0.75N hydrochloric acid to bring the reaction solution of pH 3.6. The solution is lyophilized to give 3.6 g of the desired salt.

MS(FAB): m/z 501 (M+H).

#### Example 6

35 [4S-(4a,12aa)]-9-(Acetylamino)-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

To a stirring solution of 0.488 g of product from Example 2 in 5 ml of water is added 0.50 g of sodium acateta and 0.2 ml of acetic anhydride. The reaction is stirred at room temperature for 10 minutes followed by the addition of 0.2 ml of concentrated ammonium hydroxide. After stirring 5 hours at room temperature, the reaction is treated with 0.5 ml of concentrated sulfuric acid. The reaction solution is contracted with 4 portions of n-butyl alcohol and the aqueous layer is concentrated in vacuo to dryness. The residue is triturated with 20 ml of methyl alcohol, filtered and the organic layer is concentrated in vacuo to give 0.35 g of the desided product.

45 MS(FAB): m/z 515 (M+H).

# Example 7

[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(trifluoroacety/l)amino]-2-naphthacenecarboxamide sulfate

A mixture of 0.20 g of product from Example 2 and 3.0 ml of trifluoroacetic anhydride is stirred at room temperature for 6 hours. The reaction liquid is decanted from the solid residue. The solid is dried, dissolved in 10 ml of methyl alcohol, stirred for 20 minutes and the mixture is poured into 100 ml of diethyl either. The so solid is collected and dried to give 0.16 g of the desired product. MS(FAB): ruz 569 (M+1).

#### Example 8

[4S-(4a,12au)]-7-(Diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2)

To a stirred ice cooled solution of 0.860 g of [48-(4a,12a)]-7-(diethylamino)-4-(dimethylamino)-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,-11-dioxo-2-naphthacenecarboxamide hydrochloride,
propared by the procedure described in U.S. Patent 3,26,436, dissolved in 15 mil of sulfuric acid is added
0.151 g of sodium nitrate. The mixture is stirred in the cold followed by dropwise addition to 500 ml of
of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.8 g of the
desired product as a solid.

MS(FAB): m/z 531(M+H) and 629(M+H2SO4+H).

#### Example 9

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[45-(4α,12aα)]-9-Amino-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2)

The title compound is prepared by the procedure of Example 2, using 0.82 g of product from Example 20 8, to give 0.65 g of the desired product as a solid. 'H NMR (CD<sub>3</sub>SOCD<sub>3</sub>): δ 4.25(s,1H,4-H) and 7.27(s,1H,8-H).

MS(FAB); m/z 501(M+H) and 599(M+H2SO4+H).

#### Example 10

[4S-{4\alpha,12a\alpha}]-7-(Diethylamino)-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2)

To a solution of 0.238 g of product from Example 9 in 6 ml of formic acid is added 0.035 g of sodium an acctate and 0.75 ml of acotic anhydride. The reaction mixture is stirred at room temperature for 1.5 hours then poured into 200 ml of diethyl ether. The solid is collected and dried at 50 °C to give 0.125 g of the desired product.

MS(FAB): m/z 529 (M+H) and 627 (M+H2SO4+H).

#### 35 Example 11

[4S-(4\alpha,12a\alpha)]-9-(Acetylamino)-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:2)

To a solution of 0.16 g of product from Example 9 in 0.6 ml of water is added 0.125 g of sodium acotate. After stirring for 5 mirutes, 0.05 ml of acetic anhydride is added. The reaction is stirred for 15 minutes, 0.025 ml of ammonium hydroxide is added and the stirring continued for an additional 5 minutes. The mixture is acidified with 0.125 ml of sulfuric acid, extracted with n-butyl alcohol and concentrated in vacuo. The residue is dissolved in methyl alcohol and added to diethyl either. The solid is collected and diried to give 0.10 g of the desired product.

MS(FAB): m/z 543 (M+H) and 641 (M+H2SO4+H).

#### Example 12

59 [4S-(4a,12aa)]-7-(Diethylamino)-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

A solution of 0.2 g of product from Example 10 in 10 ml of water is treated with sodium acetate to acetate to acetate. One of the mixture is extracted with chloroform. The organic extracts are dried with sodium acetate, concentrated in vacuo and the solid triturated with diethyl ether/hexane to give 0.11 g of the desired product.

MS(FAB): m/z 529 (M+H).

#### Example 13

[4S-(4a,12aa)]-9-(Acetylamino)-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

A solution of 0.25 g of product from Example 11 in 10 ml of water is treated with sodium acetate to achieve pH 6. The mixture is extracted with chloroform. The organic extracts are dried with sodium acetate, concentrated in vacuo and the solid triturated with diethyl ether/hexane to give 0.090 g of the desired product.

10 MS(FAB): m/z 543 (M+H).

#### Example 14

[4S-(4a,12aa])-4-(Dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

A solution of 0.460 g of [45-(4-a,12aa)]-4-(dimethylamino)-7-(ethylamino)-1.4.4a,5.5a,6.11,12a-octahydro-3.10,12.12a-tetrahydroy-1.11-10av-2-naphhas-enearboxamide hydrochloride, prepared by the procedure described in U.S. Patent 3.226,436, in 0.5 ml of 97% formic acid and 0.75 ml of 40% aqueous of formaldehyde is heated at reflux temperature for 2 hours, concentrated to 1/2 volume and poured into diethyl either. The resulting solid is collected, washed with diethyl either and dried to give 0.30 g of the desired product.

#### Example 15

The title compound is prepared by the procedure of Example 8, using 0.460 g of product from Example 30 14, 15 ml of sulfuric acid and 0.101 g of sodium nitrate to give 0.5 g of the desired product.

#### Example 16

[4S-(4\alpha,12a\alpha)]-9-Amino-4-(dimethylamino)-7-(ethylmethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

The title compound is prepared by the procedure of Example 2, using 1.0 g of product from Example 15, 20 ml of 2-methoxyethanol, 1.0 g of 10% palladium-on-carbon and 5 ml of 2N sulturic acid to give 0.8 g of the desired product.

#### Example 17

[48-(4\alpha,12a\alpha)-4-(Dimethylamino)-7-(ethylmethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

The title compound is prepared by the procedure of Example 3, using 1.5 g of product from Example 16, 0.235 g of anhydrous sodium acetate, 25 ml of 98% formic acid and 3.7 ml of acetic anhydride to give 1.35 g of the desired product.

# 50 Example 18

 $\label{eq:condition} \begin{tabular}{ll} $\{4S_{-}(4\alpha,12\alpha_0)\}$-9-(Acetylamino)-4-(dimethylamino)-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate $$(4B_{-}(4\alpha,12\alpha_0))$-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate $$(4B_{-}(4\alpha,12\alpha_0))$-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate $$(4B_{-}(4\alpha,12\alpha_0))$-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate $$(4B_{-}(4\alpha,12\alpha_0))$-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate $$(4B_{-}(4\alpha,12\alpha_0))$-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate $$(4B_{-}(4\alpha,12\alpha_0))$-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-letrahydro-3,10,12,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro-3,10,12a-letrahydro$ 

To a solution of 3.2 g of [45-(4₀,12a₀)]-9-amino-4-dimethylamino-1,2,3,4,4a,5,5a,6,11,11a,12, 12a-dodecahydro-10,12aa-dihydroxy-1,3,1,12-tetraoxy-2-anaphthacenecarboxamide, prepared by the procedure described in U.S. Patent 3,239,499, in 50 ml of water is added a solution of 2.5 g of sodium acetate in 12 ml of water. The mixture is cooled to 0°C and 1 ml of acetic anhydride is added with stirring. The reaction is

stirred for 20 minutes, 0.5 ml of ammonium hydroxide is added and stirred for 5 minutes. Two and one half ml of sulfuric acid is added, the reaction is extracted twice with n-butyl alcohol, the combined organic layers are washed with water and concentrated in vacuo. The residue is dissolved in methyl alcohol and added dropwise to 500 ml of diethyl other. The solid is collected and dried to give 2.3 g of the desired product. 5 MS(FAB): m2 472 (M+1) and 570 (M+1+50.4 H).

#### Example 19

[4S-(4a,12aa)]-4-(Dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-10 1,11-dioxo-2-naphthacenecarboxamide monohydrochloride

To a 0 °C solution of 1.06 g of [4S-(4a.12a)]-9-amino-4-dimethylamino-1.23,45.6, 6,11,11a,12,12a-dodecalydrof-0.12aa-diflyroxy-1.3.11 21etraoxo-2-aphihacenearboxamide, prepared by the procedures described in U.S. Patent 3,239,499, in 50 ml of formic acid is added 2.4 ml of acetic anhydride. After 1s stirring for 5 minutes, the cooling bath is removed and the reaction is stirred for 55 minutes. The mixture is added to 400 ml of diethyl either. The resulting solid is collected, washed with diethyl either and dried to give 1.1 g of the desired product. MS(FAB): m/z 458 (M+ H).

This procedure is a modification of U.S. Patent 3,239,499.

#### 20 Example 20

[4S-(4a,12aa)]-4-(Dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-iodo-1,11-dioxo-2-naphthacenecarboxamide sulfate

To a well stirred 0 °C solution of 0.278 g of product from Example 19 in 10 ml of sulfuric acid is added, in portions, 0.134g of N-iodosuccinimide. The reaction is stirred at 0 °C for 20 minutes then poured into 500 ml of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.251 g of the desired product.

MS(FAB): m/z 584 (M+H).

# Example 21

[4S-(4a,12aa)]-4-(Dimethylamino)-9-(tormylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-nitro-1,11-dioxo-2-naphthacenecarboxamide sulfate

To a well stirred 0°C solution of 0.278 g of product from Example 19 in 10 ml of sulfuric acid is added 0.3 ml of 10% nitric acid in sulfuric acid. The reaction is stirred at 0°C for 20 minutes then poured into 500 ml of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.28 g of the desired product.

40 MS(FAB): m/z 503 (M+H).

# Example 22

[4S-(4a,12aa)]-4-(Dimethylamino)-9-(formylamino)-7-[(1-methylethyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-45 3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

A solution of 0.2 g of product from Example 21 (1:2 salt), 0.5 ml of acetone, 0.5 ml of 0.5N sulfuric acid and 10 ml of 2-methoxyethanol is shaken under 35 lbs. of hydrogen, in the presence of platinum oxide, for 2 hours. The catalyst is removed by filtration, the filtrate concentrated in vacuo to 1/2 volume and poured so into diethyl ether. The resulting solid is collected and dried to give 0.135 g of the desired product.

#### Example 23

[4S-(4\alpha,12\arr)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12\arrox\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\divor\

To a well stirred solution of 0.055 g of product from Example 2, 0.200 g of sodium bicarbonate and 1 ml of N-methylpyrrolidone is added a solution of 0.011 g of methoxyacetyl chloride in 0.5 ml of acetonitrile.

After 5 minutes, the suspension is filtered and the filtrate diluted with 50 ml of tert-butyl methyl ether. The resulting solid is collected and dred to give 0.040 g of the desired product. MS(FAB): m/z 545 (M+H).

# 5 Example 24

[4S-(4a,12ax]]-4,7-Bis(dimethylamino)-9-(cyclopropylcarbonylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

70 The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 ml N-methylpyronidone, 0.010 g of cyclopropanecarbonyl chloride and 0.5 ml of acetonitrile to give 0.030 q of the desired product.

#### Example 25

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[4S-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)-9-(chloroacetylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from 20 Example 2, 0.20 g of sodium bicarbonate, 1 ml of N-methylpyrrolidone, 0.013 g of chloroacetyl chloride and 0.5 ml of accol

#### Example 26

25 [4S-(4α,12aα)]-9-[(4-Bromo-1-oxobutyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tefrahydroxy-1,11-dioxo-2-naohthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1 ml of N-methylpyrrolidone, 0.025 g of 4-bromobutyryl chloride and 0.5 ml of aceton

#### Example 27

35 [4S-(4x,12ao)]-4,7-Bis(dimethylamino) -1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(1-oxo-2-propenyi)amino]-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 ml N-methylpyrrolidone, 0.011 g of acryloyl chloride and 0.5 ml of acetonitrile to give 0.040 g of the desired product. MSIFAB: 513 (M+H).

#### Example 28

4s [4S-(4a,12aa)]-9-[[(Acetyloxy)acetyl]amino]-4,7-Bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 ml of N-methylpyprolidone, 0.013 g of acetoxyacetyl chloride on 40.5 ml of acetonitrile to give 0.040 g of the desired product. MSIFABI: m/z 573 (M+H).

# Example 29

[4S-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)-9-(phenylthioacetylamino)-1,4,4a,5,5a,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.110 g of product from Example 2, 0.40 g of sodium bicarbonate, 4.0 ml of N-methylpyrrolidione, 0.035 g of phenylthioacetyl chloride and 0.5 ml of acetoritile to give 0.075 or the desired product.

#### 10 Example 30

[48-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)-9-(pyruvylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.110 g of product from Example 2, 0.40 g of sodium bicarbonate, 1.01 in oit N-methylpyrrolidone, 0.018 g of pyruvyl chloride and 0.5 m lof acetohitrile to give 0.080 g of the desired product.

#### Evample 3

Example

[4S-(4a,12aa)]-4,7-Bis(dimethylamino)-9-(ethoxycarbonylacetylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 ml of N-methylpyrrolidone, 0.013 g of ethyl malonyl chloride and 0.5 ml of acetonitrile to give 0.035 g of the desired product.

#### Example 32

30 [4S-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)-9-(4-bromophenylacetylamino)-1,4,4a,5,5a,6,11,12-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 m of N-methylyprofildone, 0.018 g of 4-bromophenylacetyl so bloride and 0.5 ml of acetonitrile to give 0.040 g of the desired product.

#### Example 33

[4S-(4a,12aa)]-9-(Benzoylamino)-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

To a vigorously stirring solution of 0.086 g of product from Example 2, 0.085 g of sodium acetate and 3 ml of tetrahydrofuran is added 0.015 ml of benzoyl chloride and 0.25 ml of water. The reaction is stirred for 1 hour. The organic layer is decanted, washed with saturated sodium chloride, dried and concentrated in 40 vacuo. The residue is chromatographod on acid-washed diatomaceous earth using a two phase system of hexamestryl acetate2-methoxyethanchwater (50:50:17:8) to give in the second void volume 0.030 g of the desired product as an orange solid.

MSIFAB: mo? 577 (M+H)

 $^{1}H$  NMR (ds-DMSO):  $\delta$  2.45 (s,6H,C(4)N(CH<sub>3</sub>)<sub>2</sub>), 2.57(s,6H,C(7)N(CH<sub>3</sub>)<sub>2</sub>), 7.5-7.6(m,3H, benzoyl), 7.86-50 (s,1H,H-8), 7.96(d,J=7Hz,2H, benzoyl).

#### Examples 34-41 (Table I)

Substantially following the method described in detail hereinabove in Example 33 using [4S-(4α,12aa)] 9-amino-4,7-bis(dimethylamino)-1,4a, 5,5a,6,11,12a-octahydro-3,10,12.12a-tetrahydroxy-1,11-dioxo-2-naph-tacenecarboxamide sulfate (product from Example 2), the compounds of this invention listed below in Examples 34-41 are prepared.

# Table I

EX.	Ex. Acid Chloride	Product	Spectra
34	4-Methoxybenzoyl chloride	(45-(4alpha,12aalpha))]-4,7-Bis(dimethylamino)-1,4,4a,5 Bis(dimethylamino)-1,4,4a,5 Bis(dimethylamino)-1,4,4a,5 12,12a-tetrahydroxy-9-[(4-methoxybenzoy])amino]-1,11-dioxo-2-naphthacenecarbox-anide	NS(FAB): m/z 607 (M+H); <sup>1</sup> H NNR (d - DMSO); delta 2.45(e,6H, C) (c(\$) NNB-), 2.57(e,6H,C)? NNB-), 7.66(d,J-9Hz,2H of 4- methoxybenzoyl), 7.84(e,1H, H-8), 7.37(d,J-9Hz,2H of 4- methoxybenzoyl)
35	2-Methylbenzoyl chloride	[45-(4alpha,12aalpha)]-4,7- bis(dimethylamino)-1,4,4a,5 5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-9-[(2- methylbenzoyl)amino]-1,11- dioxo-2-naphthacenecarbox-	MS(FAB);m/z 591 (M+H); <sup>1</sup> H NWR (dDMSO); delta 2.52(m,12H, (Cf.)NWe 2, c(7)NWe 2), 7.25- 7.56(m,4H from 2-méthylben- zoyl), 7.98(s,1H,H-8)
36	2-Fluorobenzoyl chloride	[45-(4alpha,12aalpha)]]-4,7- Blas(dimethylamino]-5-(2- fluorobenzoyl)amino]-1,4,4a, 5,5a,6,11,12a-octahydro-1,10, 12,12a-tetrahydroxy-1,11- dioxo-2-naphthacenecarbox- amide	MS (FAB);m/z 595 (M+H); JH NWR (d_DMS); delta 2.47~2.51 (m_0H,C(4)NMe); J. 2.57(bs. 64); C(7)NMe); J. 35(m_JH from 2-fluorobenzoyl); JH from 2-fluorobenzoyl); MH from 2-fluorobenzoyl); S. 34(s_JH H-B); MH from 3-fluorobenzoyl);

# Table I (cont'd)

Ex.	Ex. Acid Chloride	Product	Spectra
37	Pentafluoro- benzoyl chloride	[45-(4alpha,12aalpha)]-4,7- Bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-cetahydro-3,10, 12,12a-tetrahydroxy-9- [(pentafluorobenzoyl)amino]- 1,11-dioxo-2-naphthacenecar- boxamide	NS(FAB):m/Z 667 (M+H); <sup>1</sup> H NNR (d -DMSO):delta 2:5 m,12H, C(Å)NNe, & C(7)NNe <sub>2</sub> ), 8.08 (s,1H,H <sup>±</sup> 8)
38	3-rrifluoro- methylbenzoyl chloride	(45-(4alpha,12aalpha)]-4,7- Bis (dimethylamino)-1,4,4a,5, Ba,6,11,12a-octanydro-3,10, 12,12a-tetrahydroxy-1,11- dixxo-9-[13-(trifluoro- methyl)benzoylamino]-2- naphthacenecarboxamide	MS (FAB):m/z 645 (M+H); H NNR (d_DMSO):delta 2.50(m/6H, C(§)NMS)); 2.57(m,6H,C(7) NNB-); 7.57(m,2H of 3-trifluoromethylbencoy)); 7.99 (m,1H of 3-trifluoromethylbencoy)); 8.28(1H of 3-trifluoromethylbencoy)); 8.28(1H of 3-trifluoromethylbencoy)); 8.31-8.48(m,2H)
39	2-Furoyl chloride	[45-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[(2-furany/carbonyl)lamino]-1,4,4,4,5,5,4,11,12a-octahydro-1,10,12,12a-tetrahydroxy-1,11-40xo-2-naphthacene-arboxamide	MS (FAB):m/z 567 (M+H); <sup>1</sup> H NWR (dDMSO):delta 2.47(m,6H, C(4)NHe), 2.565; 6H, C(1)NNe), 6.73 (s.1H of furanyl), 7.31(s,1H of furanyl), 7.31(s,1H of furanyl), 11.41-8)

# Table I (cont'd)

Ex.	Ex. Acid Chloride	Product	Spectra
0 4	2-Thiophene- carbonyl chloride	[45-(4alpha,12aalpha)]-4,7-Bis (dimethylamino)-1,4,4a, Bis (dimethylamino)-1,4,4a, 5,5a,6,1,12a-cetrahydro-3,10,12,12a-tetrahydro-y-1,11-dixco-9-([2-thianyl-carbowyl])-1,11-dixco-9-([2-thianyl-carbowyl])-1,11-dixco-9-([2-thianyl-carbowxamid])-2-naphtha-carboxamid]-2-naphtha-	MS(FAB):m/z 583 (M+H); <sup>1</sup> H NHR (dDMSO):delta 2.49(m,6H, C(2)):m,6H, 2.56(s,6H,C(7)):Ms, 3, 2, 2, m, 1H off, 1H, 1H-8); c.56(s, 1H, 1H-8); c.56(s, 1H, 1H-9); d. 1H off thisnyl); 8.01
41	4-Nitro- benzoyl chloride	[4S-(4alpha,12aalpha)]-4,7- 3hs (dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydrov- 5,10,12,12a-tertahydroxy-9- [(4-nitrobenzoyl)amino]- 1,11-dixoo-2-naphthacene- carboxamide	MS (FAB):m/z 622 (W+H); <sup>1</sup> H NNR (4_NSO):delte 2.50(m,6H, C(5) NNPe,), 2.57(s,6H,C(7) NNPe,), 7.7(s; 1.H+B), 8.20 (4_5-9Hz,2H 0.f 4-nitrobenzovi), 8.36(d,3-9Hz,2H 0.f 4-nitrobenzovi), 8.36(d,3-9Hz

# Example 42

[4S-(4\alpha,12a\alpha)]-9-[(4-Aminobenzoyl)amino]-4,7-Bisdimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate

A mixture of 0.030 g of product from Example 41, 0.010 g of 10% palladium-on-carbon, 1.5 ml of 2-methoxyethanol and 0.175 ml of 2-Methoxyethanol and 0.175 ml of 2-Methoxyethanol and 0.175 ml of 2-methoxyethanol prossure for 40 minutes. The catalyst is removed by filteration and the filtrate is concentrated in yacuo and codistilled with benzene. The city residue is dissolved in 0.5 ml of 2-methoxyethanol, precipitated with of diethyl ether and the solid collected to give 0.018 g of the desired product.

MS(FAS) rmz 592 (M+Hz)

#### Example 43

15 [4S-(4a,12aa)]-4,7-Bis(dimethylamino)-9-[[(4-dimethylamino)benzoyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

A mixture of 0.055 g of product from Example 41, 2.0 ml of 2-methoxyethanol, 0.025 g of 10% palladium-on-carbon, 0.4 ml of 2N sulfuric acid and 0.3 ml of 37% aqueous formatdehyde, in a pressure bottle, is shaken under 30 lbs. of hydrogen pressure for 50 minutes. The catalyst is removed by filtration and the filtrate is concentrated in vacuo and codistilled with heptane. The oily residue is dissolved in 1.0 ml of 2-methoxyethanol, procipitated with diethyl other to give 0.085 g of the desired product as the sulfate salt. The sulfate salt is dissolved in 0.5 ml of water and 6 ml of tetrahydrofuran followed by the addition of 0.10-g of sodium acetate. The organic layer is washed with saturated sodium chloride, dried and so concentrated in vacuo. The residue is triturated with ethyl acetate/heptane to give 0.035 g of the desired product as the free base.

MSIFABI mo & 260 (M++t)

<sup>1</sup>H NMR (d<sub>s</sub>-DMSO): δ 2.50(m,6H,C(4)NMe<sub>2</sub>), 2.57(s,6H, C(7)NMe<sub>2</sub>), 3.33(s,6H,NMe<sub>2</sub> of 4-dimethylaminobenzoyl), 7.76(s,1H,H-8), 8.20(d,J=9Hz,2H of 4-dimethylaminobenzoyl), 8.37(d,J=9Hz,2H of 4-dimethylaminobenzoyl), 6.37(d,J=9Hz,2H of 4-dimethylaminobenzoyl), 7.37(d,J=9Hz,2H of 4-d

#### Example 44

 $[7S-(7\alpha,10\alpha\alpha)]+[2-[(9-(Aminocarbonyl)-4,7-Bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-btrahydroxy-10,12-dioxo-2-naphthacenyllamino]-2-oxoethyl]carbamicacid 1,1-dimethylethyl ester$ 

A mixture of 0.850 g of product from Example 2 (as the disultate), 0.890 g of sodium acetate in 25 ml of tetrahydrofutran and 5 ml of water is stirred at 25 °C for 5 minutes. The solution is treated with 0.359 g of (succinimyloxycarbonyl)methyl carbamic acid tert-butyl ester, stirred for 2 hours and extracted with 40 chloroform. The organic layer is concentrated in vacuo to give 0.50 g of the desired product.

MSIFABI mc 250 M H-17

#### Example 45

45 [4\$-{4a,12aa}]-9-[(Aminoacetyl)amino]-4,7-Bisdimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono(trifluoroacetate)

A solution of 0.030 g of product from Example 44 and 1.0 ml of trifluoroacetic acid is maintained at 24 °C for 24 hours followed by concentrating in vacuo. The residue is triturated with methyl alcohol and the so solid collected to give 0.024 g of the desired product.

MSIFAB: m/z 530 (M+H).

#### Example 46

[4S-(4a,12aa)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

A mixture of 0.030 g of product from Example 45, 0.020 g of 10% palladium-on-carbon, 0.5 ml of 37% formaldehyde, 1.5 ml of 2-methoxyethanol and 0.175 ml of 2N sulfuric acid, in a pressure bottle, is shaken under 30 lbs, of hydrogen pressure for 40 minutes. The catalyst is removed by filtration and the filtrate is concentrated in vacuo and codistilled with benzene. The oily residue is dissolved in 0.5 ml of 2-ro methoxyethanol, precipitated with diethyl ether and the precipitate collected to give 0.025 g of the desired product.

#### Example 47

75 [4S-(4a,12aa)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6. 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(phenylsulfonyllamino]-2-naphthacenecarboxamide

A mixture of 0.30 g of product from Example 2, 0.40 g of sodium acetate in 10 ml of tetralydrofuran and 1.5 ml of water is sittered for 10 minutes under argon. The organic layer is separated, dried over anhydrous sodium sulfate and treated with 0.125 ml of benzenesulfonyl chloride and 0.80 g of sodium bicarbonate. The reaction is stirred vigorously for 1.5 hours. The organic layer is docanted and codistilled with heptane. The residue is dissolved in ethyl acetate, dried and concentrated in vacuo. The residue is chromatographed on diatomacoous earth using hexane:ethyl acetate:2-methoxyethanoliwater (35:65:15:5) to give 0.036 g of the desired product as a yellow solid.

25 MS(FAB): m/z 613 (M+H).

'H NMR (CDCl<sub>3</sub>): § 2.44(bs,6H,C(4)NMe<sub>2</sub>), 2.55(s,6H,C(7)NMe<sub>2</sub>, 7.38-7.45(m,2H,m-H's from benzenesul-tonyl), 7.52-7.56(m,1H,p-H from benzenesul-tonyl), 7.58(s,1H,H-8), 7.78(d,J=7Hz,2H,o-H's from benzenesul-tonyl).

#### 30 Examples 48-53 (Table II)

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Substantially following the method described in detail hereinabove in Example 47 using [45-(4a,12aa)]9-amino-4,7-bis(dimethylamino)-1,44a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetahydroxy-1,11-dioxo-2-naphthacenecarboxamide sultate (product from Example 2) and the appropriate alkyl, aryl or heteroarylsulfonyl
36 ohloride, the compounds of this invention listed below in Examples 48-53 are prepared.

# able II

Ex.	Sulfonyl Chloride	Product	Spectra
84	4-Chlorobenzene- sulfonyl chloride	[(4-chlorophenyl)]-9- [((4-chlorophenyl)sulfonyl)- amino]-47-bis(dimethyl) amino]-1,4 4a 5,5a,6 1],12a- tetrahydroxy-1,11-dioxo-2- naphthacenecarboxamide	MS(FAB):m/z 622 (M+H); h NNR (d=DMSO):delta 2.48(m,12H, c(\$)NMe_2), 7.16 (s,1H,H'8), 7.62(d,5Me_2), 7.16 of 4-chlorobenzenesulfonyl), 7.75(d,2+9Hz,2H of 4-chloro- benzenesulfonyl),
64	3-Nitrobenzene- sulfonyl chloride	[45-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5 Ba,6,11,12a-octahydro-1,10,12,12a-tetrahydroxy-9-[(3-nitropheny]]sulfonyllamino]-1,11-dioxo-2-naphthacenecarboxamide	MS(FAB):m/z 658 (M+H); <sup>1</sup> H NWR (dDMSO): delta 2.44-2.45 (m_12H,Cq)NMe_)
50	4-Nitrobenzene- sulfonyl chloride	[45-(4alpha,12aalpha)]-4,7- Bis (dimethylamino)-1,4,4a,5, 2a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-9- [([(4-nitropheny])-sulfony]] amino)-1,11-dioxo-2- naphthacenecarboxamide	MS(FAB):m/z 658 (H+H); H NNR (CDC1); delta 2.46(s,6H,C(4)) NNP 2); 2.58(s,6H,C(7)) NNP 2); 7.59(s,HH,He); 7.79(d,JE 9Hz,H,He); 7.79(d,JE 9Hz,H); 8.15(d,JE 9

# Table II (cont'd)

Ex.	Sulfonyl Chloride	Product	Spectra
15	2-Thiophene sulfonyl chloride	[45-(4alpha,12aalpha)]-4,7- Bis (dimethylamino)-1,4,4a,5 Sa,6,1,1,2a-octabydro-3,10, 12,12a-tetrahydroxy-1,11- dioxo-9-((2-thienyisulfony)) amino]-2-naphthacenecarbox- mide	MS(FAB):m/z 619 (M+H); H NNR (d_PNSO): delta 2.50(m,6H, (c_A)NNe, 2.54(s,6H,C(T), NNe,), 7.14(m,H of thienyl), 7.20(m,lH of thienyl), 7.51(s, H,H-G thienyl), 7.51(s,
2	2-Acetamido-4- methyl-5-thiazole sulfonyl chloride	[4S-(4alpha,12aalpha)]-9- [[(2-(decetylamino)-4-methyl- 5-thiazolyl Jaulfonyl jamino)-4,7-bis (dimethylamino)-1,4, 4,7-bis (dimethylamino)-1,4, 49,5,5,6,11,12a-cetahydro- 3,10,12,12a-tetrahydroxy-1,111-dioxo-2-naphthacenecar- boxamide	MS (FAB):m/z 691 (M+H); <sup>1</sup> H NMR (CDC), <sup>1</sup> d elta 2.15(s, 3H, thia- zoyl H <sub>2</sub> CCONH), 2.40(s, 3H, thiazoyl H <sub>2</sub> C), 2.54(s, 6H, C(4) NMe <sub>2</sub> ), 2.5 <sup>4</sup> (s, 6H, C(7) NMe <sub>2</sub> ), 7.6 <sup>5</sup> (s, 6H, C(7) NMe <sub>2</sub> ), 1H, H-8)
53	Ethane sulfonyl Chloride	[45-(4alpha,12aalpha)]-4,7-Bis(dianchylamino)-9-(ethylsulfony)]amino]-1,4,4 a,5,5 a,6,11,12a-octahydro-3,10,12,12a-tertahydro-3,10,12,12a-tertahydro-arboxamide	NS(FAB):m/z 565 (W+H); H NWR (CDC1); delta 0.88(t, 3H, CH (CDC2); 2.4-2.6(m, 12H, CH); NNG, E C(7)NNG,); 3.34(q, 2H, CH <sub>3</sub> ČH <sub>2</sub> SO <sub>2</sub> ); 7.51(s, 1H, H-B)

#### Example 54

[4S-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)-9-(tormylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinylmethyl)-2-naphthacenecarboxamide

A solution of 0.30 g of product from Example 3 and 1.2 equivalents of 30% aqueous formatdehyde in 6.0 ml of 2-methoxyethanol is treated with 5.0 equivalents of pyrrolidine. The reaction is stirred vigorously at room temperature for 1.5 hours. The crystalline solid is collected and dried to give 0.25 g of the desired product.

10 MS(FAB): m/z 584 (M+H).

#### Example 55

[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[15 [methanesulfonyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

A mixture of 0.30 g of product from Example 2, 0.40 g of sodium acetate in 10 ml of tetrahydrofuran and 1.5 ml of water is stirred for 10 minutes at room temperature under argon. The organic layer is separated, dried over sodium sulfate, filtered and treated with 0.10 ml of methanesulfonyl chloride and 0.80 ag of sodium bicarbonate. The reaction is stirred vigorously for 1.5 hours. The organic layer is decanted and codistilled with heptane. The residue is dissolved in ethyl acetate, dried and concentrated in vacuo. The crude product is chromatographed on diatomacosus earth using hexane.ethyl acetate?-methoxyethanolwater (3555:155) to give 0.016 g of the desired product as a yellow solid. MSIFAB; mc 5551 (M+19).

# Example 56

[4S-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)-9-[(methanesulfonyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(pyrrolidinylmethyl)-2-naphthacenecarboxamide

A solution of 0.30 g of product from Example 55 and 1.2 equivalents of 30% aqueous formaldehyde in 6.0 ml of 2-methoxyethanol is treated with 50 equivalents of pyrolidine. The reaction is stirred vigorously at room temperature for 1.5 hours. The crystalline solid is collected and dried to give 0.250 g of the desired

35 MS(FAB): m/z 634 (M+H).

#### Example 57

[4S-(4a,12aa)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-40 9-[[(phenylmethoxy)acetyl]amino]-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 ml of N-methylpyrrolidine, 0.018 g of benzyloxyacetyl chloride and 0.5 ml of acetoritrile to give 0.060 g of the desired product.

45 MS(FAB); m/z 622 (M+H).

#### Example 58

[7S-(7a,10aa)]-[[9-(Aminocarbonyl)-4,7-Bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino] oxo-acetic acid ethyl ester

The title compound is prepared by the procedure of Example 23, using 0.055 g of product from Example 2, 0.20 g of sodium bicarbonate, 1.0 ml of N-methylpyrrolidone, 0.015 g of ethyl oxalyl chloride and 0.5 ml of aceton

55 MS(FAB): m/z 574 (M+H).

#### Example 59

[4S-(4a,12aa)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-letrahydroxy-9-[-(hydroxyacetyl)amino]-1,11-dioxo-2-naphthacenecarboxamide

A mixture of 0.048 g of product from Example 28 and 0.6 ml of concentrated sulfuric acid is stirred at room temperature for 2 hours, poured into diethyl either and the precipitated salt collected. The salt is dissolved in 10 ml of tetrahydroturian, 0.250 g of sodium acteatio is added and the mixture strired for 1 hour. The reaction is filtered and the filtrate is concentrated in vacuo. The residue is chromatographed on a poly- (styrene-vinyl benzene)copylmer column with water-accetonitrile (1:1) to give 0.018 g of the desired product as a light yellow solid.

MSIFAB; rux 532 (M+1).

#### Example 60

[4S-(4\alpha,12a\alpha)]-9-(Acetylamino)-4-(dimethylamino)-1.4.4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamide sulfate

To a 0 °C solution of 1,06 g of (45-(4-,12a-))9-amino-4-(dimethylamino)-1,23,4,4a,5,5a,61,11,1a,12-2
12a-dodecaybrof-10,12a-a-dibydrovy-1, 3,11,12-ettapoxo-2-raphthacencarboxamide, prepared by the procedures described in U.S. Patent 3,239,499, in 50 ml of acetic acid is added 2.4 ml of acetic anhydride.

After 5 minutes, the reaction is allowed to warm to room temperature. The reaction mixture is poured into
500 ml of diethyl ether and the resulting precipitate is collected. The precipitate is washed with diethyl ether
and dried to give 1.1 g of the desired product.

MS(FAB): rex 472 (M+14)

# Example 61

[4S-(4a,12aa)]-4-(Dimethylamino)-9-(acetylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-iodo-1,11-dioxo-2-naphthacenecarboxamide sulfate

To a stirring 0°C solution of 0.278 g of product from Example 60 in 10 ml of sulfuric acid is added, portionwise, 0.1344 g of N-lodesuccinimide. After stirring at 0°C for 20 minutes, the reation mixture is poured into 400 ml of diethyl ether. The resultant precipitate is collected, washed with diethyl ether and stride to give 1.1 g of the desired product as a solid. MS(FAB): mc75 598 (M+H) and 696 (M+H;SOL+H).

# Example 62

40 [7S-(7α,10az)]-[9-(Aminocarbonyl)-4,7-Bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid methyl ester

To a room temperature mixture of 0.80 g of product from Example 2 in 2 ml of 1-methyl-2-pyroididinone is added 0.60 g of sodium bicarbonate. The mixture is stirred for 5 minutes followed by the addition of 0.12 ml of methyl chloroformate. The reaction is stirred at room temperature for 30 minutes and filtered into 200 ml of t-butyl methyl either. The resulting solid is collected and dried to give 0.370 g of the desired product. MSIFAB; mc 253 I (M+H) c

<sup>1</sup>H NMR (d<sub>6</sub> DMSO): δ 2.6(s,12H,C(4)NMe<sub>2</sub> and C(7)NMe<sub>2</sub>), 3.7(m,3H,o-CH<sub>3</sub>), 7.8(s,1H,H-3), 8.7-(s,1H,aromatic NH), 9.1(d,2H,CONH<sub>3</sub>).

# Example 63

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[7S-(7a,10aa)]-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid (2-diethylamino)ethyl ester

The title compound is prepared by the procedure of Example 62, using 0.443 g of product from Example 2, 2 ml of 1-methyl-2-pyrrolidone, 0.165 g of β-diethylaminoethyl chlorocarbonate hydrochloride and 0.443 g of sodium bicarbonate to give 0.350 g of the desired product.

<sup>1</sup>H NMR (d<sub>6</sub> DMSO): δ 1.2(m,6H,-N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.5(s,6H, C(7)NMΘ<sub>2</sub>), 2.7(s,6H,C(4)NMΘ<sub>2</sub>), 3.4-(m,2H,OCH<sub>2</sub>CH<sub>2</sub>N), 3.51 (m,4H,-N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 4.0(m,2H,-OCH<sub>2</sub>CH<sub>2</sub>N), 6.8(s,1H,H-3), 9.0(d,2H,CONH<sub>2</sub>).

# Example 64

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[7S-(7a,10aa)]-[9-(Aminocarbonyl)-4,7-bis(dirnethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid ethenyl ester

The title compound is prepared by the procedure of Example 62, using 0.189 g of product from 10 Example 2, 1 ml of 1-methyl-2-pyrrolidone, 0.75 ml of acetonitrile, 0.20 g of sodium bicarbonate and 0.037 g of vinyl chloroformate to give 0.133 g of the desired product.

MSIFABI: m/z 548 M/s +h).

<sup>1</sup>H NMR (d<sub>6</sub>DMSO + TFA): δ 4.35(s,1H,H-7), 4.6(d,1H, CH = CH<sub>2</sub>cis), 4.9(d,1H,CH = CH<sub>2</sub>,trans), 7.2(m,2H, -O-CH = CH<sub>2</sub>), 8.1(s,1H,H-3), 9.6 & 9.1(s,2H,CONH<sub>2</sub>), 9.61(s,H,aromatic NH)

#### Example 65

[7S-(7a,10aa)]-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid 2-propenyl ester

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The title compound is prepared by the procedure of Example 62, using 0.213 g of product from Example 2, 1 ml of 1-methyl-2-pyrrolidone, 0.75 ml of acctonitrile, 0.20 g of sodium bicarbonate and 0.054 g of allyl chloroformate to give 0.143 g of the desired product.

¹H NMR (d<sub>6</sub>DMSO+TFA): δ 4.65(d,2H,=CHCH<sub>2</sub>), 5.25(d,1H, CH=CH<sub>2</sub>cis), 5.4(d,1H,CH=CH<sub>2</sub>trans), 6.0-25 (m,1H,CH<sub>2</sub>=CHCH<sub>2</sub>), 8.1(s,1H,H-3), 9.1(s,1H,aromatic NH), 9.6 & 9.0(s,2H,CONH<sub>2</sub>).

Substantially following the methods described in detail hereinabove in Example 23, the compounds of this invention listed below in Examples 66-82 are prepared. Example 72 uses the appropriate anhydride rather than the acid chloride.

#### 30 Example 66

[4S-(4a,12aa)]-4-(Dimethylamino)-9-[[(4-fluorophenoxy) acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-7-iodo-1,11-dioxo-2-naphthacenecarboxamide.

# 35 Example 67

 $[7S-(7\alpha,10a\alpha)]-N-[9-(Aminocarbonyi)-4,7-Bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyi]-2-thiopheneacetamide.$ 

#### 40 Example 68

 $[4S-(4\alpha,12a\alpha)]-9-[[(Diethylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. \\$ 

#### 45 Example 69

 $[4S-(4\alpha,12a\alpha)]^{-4}-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-iodo-9-[[-(methyllhio)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide.$ 

# 50 Example 70

[45-(4\alpha,12a\alpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-[(1-methylethyl) amino]-1,11-dioxo-9-[(3,3,3-trichloro-1-oxopropyl)amino]-2-naphthacenecarboxamide.

# 55 Example 71

 $[4S-(4\alpha,12a\alpha)]+4,7-Bis(dimethylamino)-9-[(1,3-dioxo-3-phenylpropyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,12-dioxo-2-naphthacenecarboxamide.$ 

# Example 72

[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-[4-(dimethylamino)-1-oxobutyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

#### Example 73

[4\$-(4a,12aa)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[-(phenylsulfonyl)acetyl]amino]-2-naphthacenecarboxamide.

#### Example 74

[75-(7a,10aa)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a-octahydro-1,8,10a,11-tetrahydroxy-4-iodo-10,12-dioxo-2-naphthacenyl]-5-methyl-2-furanacetamide.

#### Example 75

 $[7S-(7\alpha,10a\alpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-2-thiazoleacetamide.$ 

#### Example 76

[7S-(7a,10aa)]-2-[[[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1.8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]carbonyl] benzoic acid.

#### Example 77

[7S-(7a,10ax)]-N-(9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-2-oxo-1-imidazolidineacetamide.

# Example 78

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[7S-(7a,10aa)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaconyl)-5,6-dimethylograzinecarboxamide.

# Example 79

[7S-(7a,10aa)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl)-3-methyl-3H-imidazo(4,5-b)pyridine-2-acetamide.

#### Example 80

[4S-[4α,12aα]]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentafluorophenyl)acetyl]amino]-2-naphthacenecarboxamide.

#### Example 81

[7S-(7a,10aa)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-4-iodo-10,12-dioxo-2-naphthacenyl]-4-ethyl-2,3-dioxo-1-piperazinecarboxamide.

#### Example 82

[7S-(7a,10aa)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-ethyl-2,3-dioxo-1-piperazinecarboxamide.

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#### Examples 83-86

Substantially following the methods described in detail hereinabove in Example 44, the compounds of this invention listed below in Examples 83-86 are prepared.

# Example 83

[78-(7a,10aa)]-[2-[[9-Aminocarbonyl-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-1,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl] carbamic acid 1,1-dimethylethyl ester.

#### Example 84

[75-{2(\$'),(7a\_10aa)]]-{2-{(9-(Aminocarbony)-4-(diethylamino)-7-(dimethylamino)-5,5a,6.6a,7.10,10a,12-octahydro-1,8,10a,11-leitrahydroxy-10,12-dioxo-2-naphthacenyl]amino)-1-methyl-2-oxoethyl]carbamic acid 1.1-dimethylethyl ester.

#### Example 85

# Example 86

25 [78-2(8'),(7a, 10a,)];[4-[8-(Aminocarbonyi)-4,7-bis (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyi]amino)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-4-oxobutanolc acid 1,1-dimethylethyl ester.

#### Examples 87-91

Substantially following the methods described in detail hereinabove in Example 45, the compounds of this invention listed below in Examples 87-91 are prepared.

# Example 87

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[4S-(4a,12aa)]-9-[(Aminoacetyl)amino]-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

#### Example 88

[45-(4α,9(5'),12aα)]-9-[(2-Amino-1-oxopropyl)amino]-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

#### Example 89

[4S-(4a,9(S'),12aa)]-9-[(Aminophenylacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

# Example 90

[7S-[2(5'),7a,10aa]]]-3-Amino-4-[[9-(aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl] amino]-4-oxobutanoic acid.

# Example 91

[7S-[2(S'),7\alpha,10a\alpha)]-4-[[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10, 10a-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-(dimethylamino)-4-oxobutanoic acid.

#### Examples 92-94

Substantially following the methods described in detail hereinabove in Example 47, the compounds of this invention listed below in Examples 92-94 are prepared.

# Example 92

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[48-(4\alpha,12a\alpha)]-4-(Dimethylamino)-9-[((2,2-dimethylpropyl)sulfonyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-[(1-methylethyl)amino]-1,11-dioxe-2-paohthacenecarboxamide.

# Example 93

[7S-(7a,10aa)]-4-[[[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyllamino] sulfonyllbutanoic acid.

#### Example 94

 $[4S-(4\alpha,12a\alpha)]-4-(Dimethylamino)9-[[(1,1-dimethylethyl)sulfonyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-iodo-1,11-dioxo-2-naphthacenecarboxamide.$ 

#### 20 Example 95

[4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-[[(diethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

The title compound is prepared by the procedure of Example 46, using 0.030 g of product from Example 45, 0.020 g of 10% palladium-on-carbon, 2.5 equivalents of acetaldehyde, 1.5 ml of 2-methoxyethanol and 0.175 ml of 12 nsulfure acid to give the desired product as a solid.

#### 30 Example 96

#### Dimethylaminoacetyl chloride hydrochloride

A mixture of 15 g of N.N-dimethylglycine hydrochloride (pulverized and dried in a vacuum oven at 45-55 of °C for 24 hours) and 13.85 ml of thionyl chloride is heated, very slowly, in a sand bath to 78 °C and kept at this temperature for 1 1/2 hours. Toluene is added to the mixture and the excess liquid is removed by pipette. This step is repeated several times. The solid is then transferred to a Buchner funnel, washed with methylene chloride and dried under vacuum at 50 °C for 24 hours to yield 14.2 g of the desired intermediate.

# Example 97

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acety]]amino]-1,4,4a,5,5a,6,11,12a-cctahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

To a mixture of 6.68 g of 9-amino-4,7-bis(dimothylamino)-8-demethyl-6-deoxyletracycline in 120 ml of DMPU and acctonizine is added 6.57 g of sodium cabnonale. The mixture is stirred for 5 minutes, followed by the addition of 2.83 g of product from Example 96. The reaction is stirred for 1 hour, filtered and the filtrate is added slowly to a mixture of methylene chlorida/distryl either (1200 ml/400 ml). The solid is collected, dissolved in 1250 ml methyl alcohol and added slowly to 1600 ml of methylene chlorida. The precipitate is collected, washed with diethyl ether and dried to give 5.75 g of the desired product. MS(FAB): m2.558 (M+1).

#### Example 98

[4S-(4alpha,12aalpha)]-9-[(Chloroacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

To a room temperature solution of 0.334 g of 9-amino-4.7-bis(dimethyamino)-8-demethyle-deoxyetracycline sulfate, 6 ml of 1,3-dimethyl-3,4,5,8-tetrahydro-2(1H)pyrimidinone, hereinafter called DMPU, and 2 ml of acetonitrile is added 0.318 g of sodium carbonate. The mixture is stirred for 5 minutes followed by the addition of 0.098 g of chloroacetyl chloride. The reaction is stirred for 30 minutes, filtered, and the filtrate added crowise to 100 ml of diethyl ether, containing 1 ml of 1 Mh tyforchloric acid in diethyl ether. The resulting solid is collected and dried to give 0.340 g of the desired product. MS(FAB) mz 549 (M+H).

#### Example 99

[48-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

The title compound is prepared by the procedure of Example 98, using 0.668 g of 9-amino-4,7-bis-20 (dimethylamino)-6-demethyl-6-deoxytetracycline sulfate, 6 ml of DMPU, 2 ml of acetonitrile, 0.636 g of sodium carbonate and 0.215 g of bromoacetyl chloride. Seven tenths of a gram of the desired product is obtained.

MS(FAB): m/z 593 (M+H)

# 25 Example 100

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide (free base)

To 0.20 g of product from Example 99 in 3 ml of 1,3-dimethyl-2-imidazolidenone is added 0.30 g of sodium bicarbonate. The reaction is stirred at room temperature for 15 minutes and filtered. The filtrate is added to 15 ml of diethyl ether and the resulting precipitate is collected to give 0.150 g of the desired product as the free base.

#### 35 Example 101

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide

To a solution of 5.01 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline, 100 ml of DMPU and 25 ml of acetonitrile is added 5.0 g of sodium carbonate. The reaction is stirred, under argon, at room temperature for 5 minutes, followed by the addition of 3.03 g of bromacestyl bromide. The stirring is continued for an additional hour. The solid is collected and the filtrate is added slowly to isopropyl adcoholicitethyl ether (200 ml/750 ml). The yellow solid is collected, washed with isopropanol and diethyl 4s ether to give 5.77 a of the desired intermediate.

# MS(FAB):m/z 593 (M+H).

#### Example 102

50 [4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopronyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

The title compound is prepared by the procedure of Example 98, using 1.00 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxyletracycline, 1.0 g of sodium carbonate and 0.648 g of 2bromopropionyl bromide to give 0.981 g of the desired product.

MS(FAB): m/z 607 (M+ H).

#### Example 103

[4S-(4alpha.12aalpha)}-9-[(4-Bromo-1-oxobutyl)amino]-4.7-bis(dimethylamino)-1.4.4a.5.5a.6.11.12aoctahydro-3,10,12,12a-tetrahyddroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

The title compound is prepared by the procedure of Example 98, using 1,34 g of 9-amino-4,7-bis-(dimethylamino)-6-demethyl-6-deoxytetracycline sulfate, 1.3 g of sodium carbonate, 24 ml of DMPU, 8 ml of acetonitrile and 0.389 g of 4-bromobutyryl chloride to give 1.45 g of the desired product.

#### 10 Example 104

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12aoctahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

To a solution of 0.15 g of product from Example 99 in 4 ml of DMPU is added 0.85 g of dimethylamine (40% in water). The reaction is stirred for 20 minutes followed by concentration in vacuo to remove any excess dimethylamine. The mixture is filtered and the filtrate added, dropwise, to 70 ml of isopropyl alcohol/diethyl ether (1:1). To this solution is added 1 ml of 1M hydrochloric acid/diethyl ether. The resulting precipitate is collected, washed with isopropyl alcohol and diethyl ether, and dried to give 0.11 g of the 20 desired product.

MS(FAB): m/z 558 (M+H).

#### Example 105

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25 [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[-(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride (331,256)

A mixture of 0.1258 g of product from Example 99, 5 ml of 40% methylamine in water and 5 ml of methyl alcohol, under Argon, is stirred at room temperature for 30 minutes. The excess methylamine is 30 removed in vacuo and the residue diluted with a small volume of methyl alcohol. The diluted reaction solution is added dropwise to 100 ml of diethyl ether containing 1 ml of 1M hydrochloric acid in diethyl ether and 10 ml of isopropyl alcohol. The resulting solid is collected and dried to give 0.106 g of the desired product. MS(FAB): m/z 544 (M + H).

Substantially following the methods described in detail herein above in Example 105, the compounds of 35 this invention listed below in Examples 106-125 are prepared.

s due x	D REME	Prod. of Exp.	Reactant	Rx Time	NS(FAB):
106	(TF.(Zatpha, 10ma(pha)).H.(F.(Aminocorbony)).4,7-bis(di. mathylamino).5,5,8,6,8,7,10,1ma.12-ocohydnol.g.(10,1). mathylamino).2,24dno.2,7mphthacepy().4,morpholinacar. mathylamylamida.	<b>6</b>	Morphol in s	0.5 hr.	(***)000
107	(48-(4a)pha, 12aapha) - 4,7-814(dheethylanino)-9-[((4thyl)- aaino)seetyt)aaino) - 1,4-44,5,5-6,11,12e-eeshydro-3,10,- 12,12e-eeteshydrak 12,12e-eeteshydrak	6	Ethylamina (70% in water)		(H+H)
108	(48-(4aipha,1Zamipha)) -P.[(Cyclopropylamino)acary)]amino) - 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,1Z-octahydro-5,10,- 12,12-tttcahydrosy-1,11-diaso-2-naphthacenesrboxamide di- hydrochloride.	:	Cyclopropylamine 2 hr.	2 hr.	570CM+H)
60	(65-(4alpha,  Zaalpha)) -4,7-8 iz(dimathylamino)-9-1((butyl)- nainoseeryl) amino) -1,4,4,5,5,5,4,1,12-ectahydro-3,10,12,-	:	Butylanine	2 ht.	586(#+#)
110	(66-(4alpha,)Zaalpha))-9-(((Gishtytaaino)zesty)Janinoj-4,7- bis(dinentylaninoj-1,4,4a,5,5a,4,1),Za-esthydro-3,12,12,- Zaratrahydroxy-1,11-diozo-2-naphthacencearboxamida dihy- drochloride.	\$	o iathylamine		586(N+H)
Ξ	(78-C/alpha, toastpha) w. t9-Chainecerbanyi) -4,7-biscdimathyi- asino) 5,8,4,6,8,7,10,10,12-octabydro-1,8,10s,11-tetrahydr- ory-10,12-diozo-2-napkthaenyi) -1-pyrrolidinasectanida dihy- drochioride.	8	Pyrrolidine	8. 0 F	(H+H) 785
21,	[48-(4aipha,1Zaulpha)] -4,7-Biacdinethylanino)-1,4,4a,5,5s- 6,11,1Za-octabydro-3,10,12,1Za-tatrahydroxy-9-([[[G-methyl- propyl)anino)acetyllaninoj-1,11-dloxo-2-naphthacanecarbox- anida dilydroxhorida.	2	I sobut y lamine		586(#+#)

Example	S. FEEG	Prod. of Exp.	Restant	Rx Time	MS(FAB): m/z
23	(78-(7aipha, 10aipha)) -4-(0-(nainearbony))-4,7-bis(di- methylminto)-5,5-6,6-6,7-(0) No. 12-octabyloro-1,5,10a,11- trianylminto-1,0,12-diano-2-naphthacany)-1-piper(dineacat- maide dhydrochloride.	6	Piperidine	<u>:</u>	598(#+#)
<u>:</u>	(73-(74)pha, (Oastpha)) -1-(9-(nainocarbonyi)-4,7-biz(di- methylanino) -5,5 6,6 6,7 (1,10),12-ocashyla-1,5,10,71- retrayelosy-(0,12-dioca-2-naphthaconyi) -14-inidazole-1- acatamida dihydrochiorida.	*	e lozelei	<u>;</u>	579(8+8)
115	(66-(4alpha,12alpha))-4,7-8 is (dimeshylamino)-1,4,4s,5,5s- 6,11,52a-ceshydro-3,10,12,12-tetrahydroxy-1,11-dioco-9- ((Cropylamino)ecstyllamino)-2-naphthacenesrbosanide dihydroxiloride.	2 2	Propylanine	. 75	570(#+#)
9	[45-(4alpha,12aspha))-4,7-Bistdimsthylamino)-9-[(dimsthyl-amino)acetyllamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-3,10,11,11-dioso-2-naphthacenecerboxamide disullate.		Ofsethylasine	0.5 hr.	558(N+H)
111	(45-(4sipha, 12asipha)) - 4, 7-8 iz(dimethylamino) - 9- (idimethyl- amino) meetyl] aminoj - 1, 4, 4a, 5, 5a, 6, 11, 12a- octahydoo 3, 10, 12, 12a- (etrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide.	66	Dimethylamine 0.5 hr.	0.5 hr.	558(#+#)
£	[48-(4aipha,12aipha)] -4,7-8is(dimethylamino)-0-(((heryl-amino)-0-(((heryl-amino)-0-((heryl-3-)-6)-(-)-1)-12-oceahydro-3,10-12,-12-(2e-texhydro-1-1,11-dioxo-2-naphthaenecetboxamide dihydro-chloride.		o-Kexylesine	2 hr.	614(#+H)
•	(46-(44)pha,12atlpha))-4,7-dis(dimethyluarino)-9-1(2-(dimethyluarino)-9-1(2-(dimethyluarino)-1-stopropyluarino)-1,4,4a,5,5a,6,11,12a-octahydro3,10,10,12,12a-tetrahydro3y-1,11-dioxo-2-mapthacencarboxaalda dihydrochlorida.	.01 .02	Dimethylamine (40% in water)	2.5 hr.	572(M+H)
120	(41-(4alpha, 12aalpha)). 4,7-ala(dimethytamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tarahydroay-9-([2-(mathylamino)-1- ozopropyllamino]-1,11-dlozo-2-naphthacanecarbozamide dihydro-	11, 102	Methylamine (40% in water)	2 24 	558(#+#)

e du exa	*****	Prod. of Exp.	el Resotant	Rx Time	MS(FAB):
121	(TE (Talpha, 10aalpha)) - H- (B- (dal hacarbany) - L, 7-bizdiechhyd- anton) - 1, 5a, 6, 8a, 7, 10, 10a, 12-ecchhydro - 1, 8, 10a, 11-ecchhydr- ry O, 2-dolard - Z-amphhaenyi) - tiphr-aethyd - Typroddelina- ecchiada dhydroklovida	102	Pyrrolidine	-	598(N+H)
22 .	(45-(44lphs,12aslphs))-4,7-bis(dischy(tasino)-9-(4-(dischy)-abino)-abino)-2-(di-(dischy)-abino)-1,4,4,5,5,4,6,11,12-octahydro-3,10,12,12a-terrahydroy-1,11-diono-2-naphyaeneestbossalde dihydro-chlorida.	. 103	Dimethylonine (40% in water)	2	586(N+H)
123	(45-(4alpha,12aalpha))-9-((Guty)nethylaaino)acetyllanino) 4.7-bistoliaethylanino)-1,4,4,5,5,6,6,11,12s-ocethydro-3,10,12, 12s-terahydroxy-1,11-dioxo-2-naphthacentesrboxanide dihydro- chlorida	8	N-Methylbutylemine 2 hr.	2 hr.	600(M+H)
124	(45-(4alpha,12alpha))-4,7-dis(dimethytamino)-1,4,4a,3,3a- 6,11,12a-oetahydro-3,10,12,12a-terrahydrosy-1,11-disso-0- (ff(fontytiamino)-bactyllaminol-2-naphthaeeneeebbraadde dihydrochlorids,		Anylesine	2 hr.	600(M+H)
125	[65:(dalpha, 12as(pha)]-4,7-8is(dimethytanino)-1,4,4a,5,5a-6,11,12a-octahydroxy-1,11-dioxo-9-(Chanytanthyl)anino]acety[Janino]-2-naphthacenecarboxanide	*	Benzylenina		620(#+#)

#### Example 126

[7S-(7alpha,10aalpha)]-N-(2-[(9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]glycine phenylmethyl ester

To 0.30 g of benzylglycine hydrochloride in 3 ml of 1,3-dimethyl-2-imidazolidinone is added 0.60 g of sodium bicarbonate. The mixture is stirred at room temperature for 15 minutes and filtered. To the filtrate is added 0.20 g of product from Example 100. The reaction mixture is sirred at room temperature for 1 hour and then added to diethyl either. The resulting solid is collected.

#### Example 127

[7S-(7alpha,10aalpha)]-N-(2-[(9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-oxoethyl]glycine

One-tenth of a gram of product from Example 126 in 10 ml of monomethyl ethylene glycol is reduced calalytically, in a Parr shaker, with 0.10 g of 10% palladium on carbon, at 30 psi of hydrogen, for 2 hours. The reaction mixture is filtered and the filtrate concentrated to give 0.050 g of the desired product. CHMS: miz 588 (M + H).

# General Procedure for the Preparation of Mannich Bases

A mixture of 0.5 g of product from Example 117, 3 ml of t-butyl alcohol, 0.55 ml of 37% formaldehyde, and 0.55 ml of pyrolidine, morpholine or piperidine is stirred at room temperature for 30 minutes bade by heating at 100 °C for 15 minutes. The reaction mixture is cooled to room temperature and triturated with diethyl ether and hexane. The solid is collected, washed with diethyl ether and hexane, and dried to give the desired product. In this manner the following compounds are made:

#### 30 Example 128

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahy dro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrol idinyl-methyl)-2-naphthacenecarboxamide

# 35 Example 129

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(di methylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octa hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(4-morph olinyl-methyl)-2-naphthacenecarboxamide

# 40 Example 130

[4S-(4alpha,12aaipha)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-piperi dinylmethyl)-2-naphthacenecarboxamide

#### 45 Example 131

[75-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-napthacenyl]-1-azetidineacetamide

The title compound is prepared by the procedure of Example 105 using 0.20 g of product form Example 99, 0.50 g of azeiddine and 5 ml of DMPU to give 0.126 g of the desired product. MSifABi: m/z 570MH-HI.

# Example 132

[4S-(4alpha,12aalpha)]-9-[[(Cyclobutylamino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

To a solution of 0.200 g of 9-(bromoacetylamino)-7-dimethylamino-6-demethyl-6-deoxyletracycline in 2 ml of 1,3-demethyl-2-imidazoidinone is added 0.1 ml of cyclobutylamine. The resulting solution is stirred at room temperature for 45 minutes and then added to 50 ml of diethyl either. An oil layer is formed and the diethyl ether layer is decanted and the oil is dissolved in 5 ml of 0.1 N methanolic hydrogen chloride. The resulting solution is added to 50 ml of diethyl ether, yielding 0.050 g of solid.

MSi(FAB): rx 584(M+H)

#### Claims

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#### 15 1. A compound of the formula:

35 wherein:

X is selected from amino, NR<sup>1</sup>R<sup>2</sup>, or halogen; the halogen is selected from bromine, chlorine, fluorine or loding.

and when  $X = NR^1R^2$  and  $R^1 = hydrogen$ ,

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R<sup>1</sup> = methyl or ethyl,

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R1 = n-propyl,

R<sup>2</sup> = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R1 = 1-methylethyl,

R<sup>2</sup> = n-butyl, 1-methylpropyl or 2-methylpropyl; and when R<sup>1</sup> = n-butyl,

R<sup>2</sup> = n-butyl, 1-methylpropyl or 2-methylpropyl; and when R<sup>1</sup> = 1-methylpropyl,

 $R^2 = 2$ -methylpropyl;

R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0.

R¹ is selected from hydrogen; aminor, monosubstituded amino selected from straight or branched (Cr.-C)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylathyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (Cr-C)alkyl group selected from methyl, ethyl, n-proppyl, 1-methylethyl, n-butyl, 1-methyl-propyl, 2-methylpropyl or 1,1-dimethylethyl; (Ca-Co-c)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (Ca-Co-c)cycloalkyl group (substitution selected from (Cr-Ca)alkyl, cyano, amino or (Cr-Ca)alkyl); (Ca-Ca-c)aryl group (substitution selected from thenyl, a-naphthyl or β-naphthyl; substituted (Ca-Ca)alkovy, trihalo(Gr-Ca)alkyl, ntrina, mnino, cyano, (Cr-Ca)alkovy, drihaloghyl, (in-ca)alkyl, antiro, amino, cyano, (Cr-Ca)alkovy, trihaloghyl, (in-ca)alkyl, antiro, amino, cyano, (Cr-Ca)alkovy; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)alkov; (Cr-Ca)al

selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a-amino-(C.-C.) alklyl group selected from aminomethyl, a-aminoethyl, a-aminopropyl or a-aminobryly, catoxy(C.-C.)-alklytamino group selected from aminoacetic acid, a-aminobutyric acid or a-aminopropionicacid and their optical isomers; (C.-C.) arallylamino group; (G.-C.) alkorycarbonylamino substituted (G.-C.) alklyl group, selected from hisylf or a-hydroxyrinonyl; a-hydroxyric-C.5 alklyl group selected from hydroxyymethyl, a-hydroxyethyl or a-hydroxy-1-methylethyl or a-hydroxyric-pyl; a-emercapto-group; halosolicted from mercapbomethyl, a-mercapto-in-thyl-mercapto-in-methylethyl or a-mercapto-group; halo-(G.-C.) alklyl group; a heterocycle group selected from a fivo membered aromatic or saturated ring with one N, O, S or Se heteroaction optionally having a banzo or pyrido ring fused thereto:

Ø .. Ø

#### Z = N. O. S or Se .

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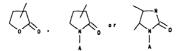
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

#### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_2)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_2)$ alkylamino or carboxyl;  $(C_7-C_9)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or So heteroatoms, or a six membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, tifluoroacetyl, (C<sub>2</sub>-C<sub>4</sub>)-cycloalkylcarbonyl, (C<sub>2</sub>-C<sub>1</sub>)aroyl selected from benzoyl or naphthoyl, halo substituted (C<sub>2</sub>-C<sub>1</sub>)aroyl, (C<sub>1</sub>-C<sub>2</sub>)alylongov, or (heterocycloglachonyl, the heterocyclos selected from a five membered aromatic or saturated ring with one N, O, S or So heteroatom optionally having a benzo or pyrido ring fused therefor:



#### Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

#### $Z \text{ or } Z^1 = N. O. S \text{ or } Se$ .

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_1)alkyl; C_5-aryl;$  substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)alkoxy,$  trihalo $(C_1-C_3)alkyl,$  nitro, amino, cyano,  $(C_1-C_4)alkoxycarbonyl,$   $(C_1-C_3)alkyl,$  group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-



#### Z = N. O. S or Se 1:

(C1-C1-plakky), Gymup; C3-eryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C1-C1-plakky), nitro, cyano, thiol, amino, carboxy, df(C1-C3-plaky)amino); (C2-C1-plaky), arranged property, or (C2-C1-plaky), cyano, carboxy, or (C3-C1-plaky) selected from phenyl, a-naphthyl or β-naphthyl); R\*R\*amino(C1-C1-plaky), cyano, carboxy, or (C3-C1-plaky) carboxy, or (C3-C1-plaky), carboxy), or R\*R\* is (CH2), n = 2-6, or -(CH2), W(CH2); wherein W is selected from -N(C1-C3-plaky), carboxy), carboxy, ca

R<sup>4</sup> is selected from hydrogen; amino; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from methyl,

ethyl, n-propyl, 1-methylethyl, n-bubly, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; (G--C<sub>2</sub>)-cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C<sub>2</sub>-C<sub>2</sub>)-cycloalkyl group (substitution selected from (G--C<sub>2</sub>)akyl), cyano, amino or (G--C<sub>2</sub>)axyl); (C<sub>2</sub>-C<sub>1</sub>)axyl group selected from phenyl, α-naphthyl or β-naphthyl; substituted(G-<sub>2</sub>-G<sub>1</sub>)axyl group (substitution selected from halo, (G--C<sub>2</sub>)akydx, into, amino, cyano, (C--C<sub>2</sub>)alkydx), mino or carboxyl; (G--C<sub>2</sub>)arkyl group; acyloxy or haloacyloxy group selected from benzoyl propionyl, chloroacetyl, trichloroacetyl, (G--C<sub>2</sub>)cycloalkylcar-bonyl, (G--C<sub>10</sub>)arcy) selected from benzoyl or naphthyl, halo substituted (G--G<sub>1</sub>)arcy), (G--C<sub>2</sub>)arkylbenzoyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se .

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring tused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched ( $C_1$ - $C_4$ )alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo,( $C_1$ - $C_4$ )alkoxy, trihalo( $C_1$ - $C_3$ )alkyl, nitro, amino, cyano, ( $C_1$ - $C_4$ )alkoxycarbonyl. ( $C_1$ - $C_4$ )alkylamino or carboxy); ( $C_7$ - $C_9$ )aralkyl group selected from benzyl, 1-phenylethyl. 2-phenylethyl. 2-phenylethyl. 2-phenylethyl. 2-phenylethyl.

Z = N, O, S or Se ,

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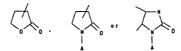
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or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(G_1-G_2)$ alkoxy, trihalo $(G_1-G_2)$ alkyl, nitro, amino, cyano,  $(G_1-G_2)$ -alkoxycarbonyl,  $(G_1-G_2)$ -alkyl amino or carboxy);  $(C_2-C_2)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms, and an adjacent appended O heteroatom; hydroxy group; mercapto group; mono- or di-straight or branched chain (C<sub>1</sub>-C<sub>2</sub>)alkylamino group selected from methyl, ethyl, e-hydroxy, 1-methylproxyl, 2-methylproxyl, 2-methylproxyl, 2-methylproxyl, 2-methylproxyl, 3-methylputyl, 2-dimethylbutyl, 2-dimethylbutyl, 2-dimethylbutyl, 1,1-dimethylproxyl, 2-dimethylbutyl, 1,1-dimethylproxyl, 2-dimethylbutyl, 1,1-dimethylproxyl, 3-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 0-methylpentyl, 1,1-dimethylbutyl, 0-methylpentyl, 1,1-dimethylbutyl, 0-methylpentyl, 3-methylpentyl, 3-methylpentyl, 3-methylpentyl, 0-methylpentyl, 0-me



Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or } S_{\theta}$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo  $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl.  $(C_1-C_3)$ alkylamino or carboxy);  $(C_2-C_3)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenyl

or a six membered aromatic ring with one to three N, O, S or Se hetenoatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (Ci-Ci-Jalkovycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino; (Ci-Ci-Jalkoxycarbonyl group selected from methoxycarbony, ethoxycarbonyl, straight or branched propoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched (Ci-Ci-Jalkoy) selected from methyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 2-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or RRP is (CH<sub>p</sub>), n = 2-8, or 3-methylpropyl or 3-methy

-(CH<sub>2</sub>)<sub>2</sub> W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>2</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>2</sub>)alkyl], O or S; or R\*P\*aminoxy group, wherein R\*P\* is a straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or R\*P\* is (CH<sub>2</sub>)<sub>2</sub>, n = 2-8, or

 $-(CH_2)_2W(CH_2)_2 - \text{ wherein } W \text{ is selected from } -N(C_1-C_3)\text{alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or <math>(C_1-C_3)\text{alkyl], O or S;}$ 

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with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

#### Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

#### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

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(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_2)$ alkoxy, trihalo( $C_1-C_2$ )alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_2)$ -alkylamino or carboxy);  $(C_2-C_2)$ -aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; RPR\*amino(C)-cJajakovy group, wherein RPR\* is a straight or branched (C)-cJajakovj selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPR\* is (CH<sub>2</sub>), n-2-8, or -(CH<sub>2</sub>), W-(CH<sub>2</sub>), w-(CH<sub>2</sub>), w-(CH<sub>2</sub>), w-(CH<sub>2</sub>), w-(CH<sub>2</sub>), w-(CH<sub>2</sub>), w-(C), w

# and when $R = R^4'(CH_2)_nSO_2$ and n = 1-4,

and wint in — In (Cryp.30.02- ard In — 14-),

R\* is selected from hydrogen; straight or branched (Cr-C<sub>4</sub>)alkyl group selected from methyl, ethyl, npropyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; (Cr-C<sub>4</sub>)carboxyalkyl
group; (Cs-C<sub>5</sub>-Cyc)colalkyl group selected from cyclopropyl, cyclobutyl, cyclopontyl or cyclopentyl, or cyclopentyl or cycl

from -N(C<sub>1</sub>-C<sub>2</sub>)alkyl (straight or branched]. -NH. -NOB (B is selected from hydrogen or (C<sub>1</sub>-C<sub>2</sub>)alkyl), O r S; or  $\mathbb{R}^{n}$ C aminoxy group, wherein  $\mathbb{R}^{n}\mathbb{R}^{n}$  is a straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-bubyl, n-bub

(C<sub>1</sub>-C<sub>2</sub>)alkyllthic group selected from methylthic, ethylthic or n-propylthic, C<sub>2</sub>-arylthic group selected from phenylthic or substituted phenylthic (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, cyano, thicl, amino, carboxy, dl(C<sub>1</sub>-C<sub>2</sub>)alkylamino), (C<sub>2</sub>-C<sub>3</sub>)aralkylthic group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring tused thereto:

Z = N, O, S or Se .

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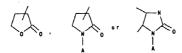
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>5</sub>)-alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alxylamino or carboxyl; (C<sub>2</sub>-C<sub>6</sub>)aralkyl group selected from benzyl, 1-ohenylethyl 2-ohenylethyl or ohenylethyl or ohenylethyl 2-ohenylethyl or ohenylethyl or ohenylet

or a six membered aromatic ring with one to three N, O,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom, hydroxy group, mercapto group; mone- or di- straight or branched (Ci-Ca)alkylamino group selected from methyl, ethyl, e-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylpropyl, 2-dimethylputyl, 2-dimethylbutyl, 2-methylputyl, 1,1-dimethylputyl, 2-dimethylbutyl, 2-dimethylputyl, 2-dimethylputyl, 1,3-dimethylputyl or 1-methyl-tetyl-propyl amino; halo(Ci-Ca)alkyl group; acyl or haloacyl group selected from benzoyl or naph-thoyl, halo substituted (Ci-Ci-o)aroyl, (Ci-Ci-o)aroyl, (Ci-Ci-o)aroyl, chloroacetyl, thiluoroacetyl, choroacotyl, Ci-Ci-o)aroyl, (Ci-Ci-o)aroyl, or (heterocycle)carbonyl, the heterocycle selected from a five memberod aromatic or saturated ring with one N, O, S or Se heteroactom optionally

having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se .

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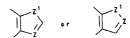
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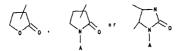
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₄-aryl; substituted C₅-aryl (substitution selected from halo,(G₁-C₄)alkoxy, trihalo(G₁-C₃)alkyl, nitro, amino, cyano, (G₁-C₄)alkoxycarbonyl, (C₁-C₃)alkylamino or carboxyl; (C₂-C₃)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylptropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (Cg-Cc)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched buttoxycarbonyl.

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; (C<sub>5</sub>-C<sub>1</sub>)akyl group selected from phenyl, a-naphthyl or β-naphthyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or S6 heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se.

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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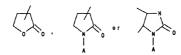
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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $(C_1-C_4)alkyt$ ;  $C_5-aryt$ ; substituted  $C_6$ -aryt (substitution selected from halo, $(C_1-C_4)alkoxy$ , trihalo $(C_1-C_3)alkyt$ , nitro, amino, cyano,  $(C_1-C_4)alkoxy$ -athoxytochonyl.  $(C_1-C_4)alkoxy$ -athoxytochonyl.  $(C_1-C_4)alkyt$ -anino or carboxy);  $(C_2-C_5)aralkyt$  group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl.

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or  $-(CH_2)_nCOOR^2$  where n=0.4 and  $R^2$  is selected from hydrogen; straight or branched  $(C_1-C_2)_{alk}yl$  group selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(C_6-C_{10})_{aryl}$  group selected from phenyl, a-naphthyl or R-naphthyl; or R-naphthyl or R-nap

R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; (C<sub>5</sub>-C<sub>1</sub>)ayrl group selected from phenyl, *c*-naphthyl or *β*-naphthyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



## Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

## $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

- (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alky<sub>2</sub>, trihalo(C<sub>1</sub>-C<sub>2</sub>)alky<sub>3</sub>, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoycyacrbonyl, (C<sub>1</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
- or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or -(CHb<sub>2</sub>),COOR<sup>2</sup> where n = 0-4 and R<sup>2</sup> is selected from hydrogen; staight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl selected from methyl, ethyl, erpooyl of -methylethyl; or (C<sub>3</sub>-C<sub>1</sub>) anyl selected from phyl, a-naphthyl or β-naphthyl; with the proviso that R<sup>2</sup> and R<sup>2</sup> cannot both be hydrogen;
  - or R° and R° taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n=0-1, -NH, -N(0;-C<sub>3</sub>)<sub>3</sub>lk(Ny, coygen, sulfur or substituted congeners selected from (C or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.
- The compound according to Claim 1, wherein: X is selected from amino, NR1R2, or halogen; the halogen is selected from promine, chlorine, fluorine or iodine; and when X = NR1R2 and R1 = hydrogen.
  - R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl, and when R<sup>1</sup> = methyl or ethyl,
  - R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
  - R is selected from  $R^4$  (CH<sub>2</sub>)<sub>n</sub>CO- or  $R^4$  (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-; and when  $R = R^4$  (CH<sub>2</sub>)<sub>n</sub>CO- and n=0,
  - Rt is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C1-C<sub>5</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C1-C4)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; (C3-C6)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group (substitution selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo (C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo (C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano. (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); a-amino(C1-C4)alkyl group selected from aminomethyl, a-aminoethyl, a-aminopropyl or a-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, α-aminobutyric acid or α-aminopropionic acid and their optical isomers; (C<sub>7</sub>-C<sub>5</sub>)aralkylamino group; (C1-C4)alkoxycarbonylamino substituted (C1-C4)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy-1-methylethyl or α-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se .

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo, $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl.  $(C_1-C_3)$ alkylamino or carboxy);  $(C_7-C_9)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, tifuoroacetyl, (G-C<sub>4</sub>)-cycloalky/carbonyl, (G-C<sub>4</sub>-G-g)aroyl selected from benzoyl or naphthoyl, halo substituted (G-C<sub>4</sub>-C<sub>1</sub>)aroyl, (G-C<sub>4</sub>-G)aybrozyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

(A is selected from hydrogen; straight or branched  $(C_1 \cdot C_4)$ alkyl;  $C_5 \cdot aryl$ ; substituted  $C_5 \cdot aryl$  (substitution selected from halo, $(C_1 \cdot C_4)$ alkoxy, trihalo $(C_1 \cdot C_5)$ alkyl, nitro, amino, cyano,  $(C_1 \cdot C_5)$ alkoxycarbonyl,  $(C_1 \cdot C_5)$ alkylamino or carboxy);  $(C_2 \cdot C_5)$ aralkyl group selected from benzyl, 1-phonylethyl, 2-phenylethyl or phonyloropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (Cr-C<sub>4</sub>)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, vinyl or substituted vinyl group [substitution selected from (Cr-C<sub>2</sub>)alxyl group, halogen, (Cr-C<sub>2</sub>)alxy group selected from phenyl, α-naphthyl, β-naphthyl, substituted (Cr-C<sub>2</sub>)alxyl group (substitution selected from phenyl, (Cr-C<sub>2</sub>)alxyly, halocycarbonyl, (Cr-C<sub>2</sub>)alxyly, halocycarbonyl, (Cr-C<sub>2</sub>)alxyly, halocycarbonyl, (Cr-C<sub>2</sub>)alxyly, halocycarbonyl, (Cr-C<sub>2</sub>)alxyly, proup, a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyridot ring thas selected from which are selected from the s

Z = N. O. S or Se 1:

(G-C-)alkovy group: C<sub>2</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (G-C-)alkyl, nitro, cyano, thiol, amino, carboxy, d(G-C-)alkylamino); (G-C-G-)alkylamino); (G-C-G-)arkylamino); (G-C-)arkylamino); (G-C-)arkylamino);

R<sup>1</sup> is selected from hydrogen; (G.-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; amino; monosubstituted amino selected from straight or branched (G--C<sub>2</sub>)alkylamino, cycloburylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethylamino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-midazolyl, 1-pyrucyll, 1-f(1,23-ritazolyl) or 4-f(1,24-ritazolyl) (G--C<sub>1</sub>-p)alkyry group selected from phenyl, α-naphthyl or β-naphthyl; substituted (Gc--C<sub>1</sub>-G)aryl group (substitution selected from halo, (C--C<sub>2</sub>-C<sub>3</sub>)alkyry carbonyl, (G--C<sub>3</sub>-C<sub>3</sub>)aryl group selected from panon, cyano, (G--C<sub>3</sub>)alkovy, (G--C<sub>3</sub>-C<sub>3</sub>)aryl group carboxy); acyloxy or haloacyloxy group selected from acetyl, propionyl, chloroacetyl, trichloroacetyl, (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl, (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl, (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl, (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl, (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl selected from bonzoyl or naphthyl, halo substituted (G--C<sub>3</sub>-G)aryl), (G--C<sub>3</sub>-G)aryl-group selected from a tive membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fixed theretor.

## Z = N, O, S or Se .

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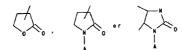
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

# $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



# (A is selected from hydrogen; straight or branched $(C_1-C_4)$ alky); $c_2-ary$ ; substituted $C_4$ -aryl (substitution selected from halo,( $C_1-C_4$ )alkoxy, thhalo( $C_1-C_4$ )alkyl, nitro, amino, cyano, $(C_1-C_4)$ alkoxycarbonyl, $(C_1-C_4)$ alkylamino or carboxy); $(C_2-C_4)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropi)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C1-C1)alkoxy group; RaRbamino(C1-C1)alkoxy group, wherein RaRb is a straight or branched (C1-C1)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n = 2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_3)$ alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or R9R9aminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2), n = 2-6, or -(CH2)2W-(CH2)2wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; C<sub>6</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di(C1-C3)alkylamino); (C1-C3)alkylthio group selected from methylthio, ethylthio, propylthio or allylthio; C6-arylthio group selected from phenylthio or substituted phenylthio (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); C<sub>6</sub>-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

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Z = N, O, S or Se

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or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido fused thereto:

Z or  $Z^1 = N$ , O, S or Se

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_2-aryl$ ; substituted  $C_6-aryl$  (substitution selected from halo, $(C_1-C_2)$ alkoxy, trihalo $(C_1-C_2)$ alkyl, nitro, amino, cyano,  $(C_1-C_2)$ alkoxycarbonyl.  $(C_1-C_2)$ alkylamino or carboxy);  $(C_2-C_2)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyloropyl)

or a six membered aromatic ring with one to three N, O,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; hydroxy group; a-hydroxy[Ci-C<sub>2</sub>)alkyl group; selected from hydroxyn-t-methylethyl or a-hydroxyproxyl; halo(Ci-C<sub>2</sub>)alkyl group; acyl or haloacyl group selected from acetyl, propionly, chloroacetyl, trifluoroacetyl, (Ca-C<sub>2</sub>)cycloskylcarbonyl, (C-C<sub>1</sub>)alkyl group; acyl or haloacyl group selected from benzoyl or naphthoyl, halo substituted (C<sub>2</sub>-C<sub>1</sub>)aroyl, (Ca-C<sub>2</sub>)cycloskylcarbonyl, C-C<sub>1</sub>)alkyl benzoyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched ( $C_1$ - $C_4$  balkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo,( $C_1$ - $C_4$ )alkoxy, trihalo( $C_1$ - $C_3$ )alkyl, nitro, amino, cyano, ( $C_1$ - $C_4$ )-alkoxycarbonyl, ( $C_1$ - $C_3$ )alkylamino or carboxy); ( $C_7$ - $C_9$ )aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylgropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C<sub>1</sub>-C<sub>4</sub>)alkovycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino; and when R = R\*(CH<sub>5</sub>,SO<sub>5</sub>) and n = 0.

R<sup>4</sup> is selected from amino; monosubstituted amino selected from straight or branched (c;--c<sub>2</sub>)-alkylamino, cycloptorylamino, benzylamino or phenylamino; disbustituted amino selected from dimethylamino, cycloptorylamino, benzylamino or phenylamino; disbustituted amino selected from dimethylamino, diethylamino, ethyl(-methylathylamino, monomethylbenzylamino, branchod (G,-C<sub>2</sub>)alkyl group selected from methyl, 1-pyrolyl, 1-(1,2,3-triazolyl); straight or branchod (G,-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-pyrolyl or 1-methylathyl; (G,-C<sub>2</sub>)-alkyl group selected from phenyl, a-naphthyl or 2-maphthyl; substituted (C<sub>2</sub>-C<sub>2</sub>)alyl group (substitution selected from hate, (G,-C<sub>2</sub>)alkoyyarbonyl, (G,-C<sub>2</sub>)-alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or S enherostom optionally having a beazo or pyrido ring lused therato:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

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 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

10 (A is selected from hydrogen; straight or branched (G₁-G₄)alkyl; G₅-aryl; substituted G₅-aryl (substitution selected from halo,(G₁-G₄)alkoy, trihalo(G₁-G₄)alkyl, nitro, amino, cyano, (G₁-G₄)alkoyacrobonyl, (G₁-G₄)alkylamino or carboxy); (C₂-C₂)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; and when  $R = R^{\alpha}(CH_{2},SO_{2})$  and n = 1.4,

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propy) or 1-methylethyl; (C<sub>5</sub>-C<sub>1</sub>-)ayrıl group; selected from phenyl, a-naphthyl or β-naphthyl; (C<sub>7</sub>-C<sub>5</sub>)-aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ ,

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

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(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_5$ -aryl (substituted from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_2)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarboryl,  $(C_1-C_2)$ -alkyl, amino or carboxy);  $(C_7-C_5)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl,

or a six membered aromatic ring with one to three N, O, S or S heteroatoms, or a six membered saturated ring with one or two N, O, S or S heteroatoms and an adjacent appended O heteroatom; or  $-(CH_2)_cOOR^2$  where n=0.4 and  $R^2$  is selected from hydrogen; straight or branched  $(C_1-C_2)$ alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(C_4-C_1)$ aryl group selected from phenyl, a-naphthyl or A-na

 $R^6$  is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propy) or 1-methylethyl; (C<sub>2</sub>-C<sub>1</sub>)ayrl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl; (C<sub>7</sub>-C<sub>2</sub>)-aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se ,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ ,

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)akyl; C_5-aryl;$  substituted  $C_5$ -aryl (substitution selected from halo, $(C_1-C_4)akxyl;$  rithalo $(C_1-C_3)akyl;$  nitro, amino, cyano,  $(C_1-C_4)-akxyl;$  (C<sub>1</sub>-C<sub>2</sub>)akxylamino or carboxy);  $(C_2-C_5)aralkyl$  group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or  $(Gt_0)_nCOOR^{\gamma}$  where n=0.4 and  $R^{\gamma}$  is selected from hydrogen; straight or branched  $(G_1-G_2)$ alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(G_2-G_1)$ alkyl selected from phenyl,  $\alpha$ -naphthyl or 8-naphthyl with the provise that  $R^{\alpha}$  and  $R^{\alpha}$  cannot both be hydrogen:

or R<sup>5</sup> and R<sup>5</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>-W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>h</sub> and n = 0-1, -NH, -N(G,-C<sub>2</sub>)<sub>a</sub>lkyl (straight or branched). -N(G,-C<sub>2</sub>)<sub>a</sub>lkov<sub>2</sub>, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pytrollidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

 The compound according to Claim 1, wherein: X is selected from amino, NR<sup>1</sup>R<sup>2</sup>, or halogen; the halogen is selected from bromine, chlorine, fluorine or iodine;

and when X = NR1R2 and R1 = hydrogen.

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 $R^2$  = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when  $R^1$  = methyl or ethyl,

R2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R4 is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C1-C<sub>6</sub>) alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>3</sub>-C<sub>5</sub>)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, trihalo (C<sub>1</sub>-C<sub>3</sub>) alkyl, nitro, amino, cvano, (C<sub>1</sub>-C<sub>4</sub>) alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); \( \alpha \)-amino(C1-C4)alkyl group selected from aminomethyl, \( \alpha \)-aminoethyl, \( \alpha \)-aminoethyl, \( \alpha \)aminopropyl or α-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid, αaminobutyric acid or α-aminopropionic acid and their optical isomers; (C<sub>7</sub>-C<sub>9</sub>)aralkylamino group; (C<sub>1</sub>-Ct)alkoxycarbonylamino substituted (C1-Ct)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy-1methylethyl or α-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } S_{\theta}$ ,

- (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-anyl; substituted C<sub>6</sub>-anyl (substitution selected from hab.(G<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(G<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (G<sub>1</sub>-C<sub>5</sub>) alkoxycarbonyl, (G<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-chenylethyl, 2-chenylethyl, 2-chenylet
  - or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, trifluoroacetyl, (C<sub>3</sub>-C<sub>4</sub>)-cycloally/carbonyl, (C<sub>6</sub>-C<sub>1</sub>-g)-groyl selected from benzoyl or naphthoyl, halo substituted (C<sub>6</sub>-C<sub>1</sub>-g)-groyl, (C<sub>1</sub>-C<sub>4</sub>-Q)-groyl, ergorety-cyclo-glorohyr, the heterocycles selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

## Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

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 ..  $\downarrow$ 

# $Z \text{ or } Z^1 = N, O, S \text{ or Se}$

- (A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substituted from halo, $(C_1-C_4)$ alkoxy, trihaio $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_3)$ alkylamino or carboxy);  $(C_7-C_3)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-p
- or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C1-C4)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl; vinyl or substituted vinyl.

group substitution selected from (G.-C.)alkyl group, halogen, (G.-C.)alyl group selected from phenyl, -naphthyl, \(\theta\)-naphthyl, substituted (G.-C.)alyl group (substitution selected from halo, (G.-C.)alkyc, trihalo(G.-C.)alkyl, nitro, amino, cyano, (G.-C.)alkoxycarbonyl, (G.-C.)alkylamino or carboxy), halo(G.-C.)alkyl group, a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroation optionally having a benze or pyrido ring fused thereigh.

Z = N. O. S or Se 1:

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(Ci-Ci,)alk'oxy group: Ci-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo. (Ci-Ci,)alkyl, nitro, cyano, thiol, amino, carboxy, d(Ci-Ci,)alkylamino); (Cj-Ci,)-Ci, aralkyloxy group; vinyiboxy or substituted winyloxy group (substitution selected from (Ci-Ci,)alkyl, cyano, carboxy, or (Ci-Ci,)alxyl selected from phenyl, a-naphthyl or β-naphthyl); RPPPamino(Ci-Ci,)alkyl, group, wherein RPP is a straight or branched (Ci-Ci,)alkyl, selected from methyl, athyl, n-propyl, 1-methylathyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPPR is (Cht), n=2-8, or -(Cht), W(Cht), wherein W is selected from -N(Ci-Ci,)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (Ci-Ci,)alkyl, or S; or RPPPaminoxy group, wherein RPPR is a straight or branched (Ci-Ci,)alkyl, selected from methyl, athyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPPR is (Cht), n=2-8, or -(Cht), W(Cht), wherein W is selected from -N(Ci-Ci,)alkyl [Straight or branched], -NH, -NOB [B is selected from hydrogen or (Ci-Ci,)alkyl], O or S; and when R = Rt'(Cht). Och and n=1-4.

It is selected from hydrogen: (C.-C.)alkyl group selected from methyl, ethyl, n-propyl or 1-methylothyl; amino; monosubstituted amino selected from straight or branched (C-Cc)alkylamino, cyclopropylamino, cyclopropylamino, cyclopropylamino, opclopropylamino, benzylamino or phonylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-midazolyl, 1-pyrolyl, 1-1(2.3-diracyly) or 4-f1.24-friazolyl); C-C-cla parly group selected from phenyl, --naphthyl or β-naphthyl; substituted (C<sub>2</sub>-Ct<sub>1</sub>)aryl group (substitution selected from halo, (C-C-Jalkoy, trihalo(C-C)alkyl, nitro, amino, cyano, (C-C-Jalkoyn-carbony), (C-C-Jalkylamino or carboxy); acyloxy or haloacyloxy group selected from acetyl, propionyl, chloroacetyl, ficthoroacetyl, (Ca-C<sub>2</sub>)cycloalkylcarbonyl), (Ca-C<sub>3</sub>)carbonyl, (Ca-C<sub>3</sub>)car



Z = N, O, S or Se ,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent

appended O heteroatom:

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(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_5$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_4)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_3)$ -alkylyamino or carboxy);  $(C_2-C_6)$ -aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl or phenylptopyl)

or a six membered aromatic ring with one to three N. O. S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C1-C4)alkoxy group; C6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl,nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); RaRbamino-(C1-C4) alkoxy group, wherein RaRb is a straight or branched (C1-C4) alkyl selected from methyl, ethyl, npropyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2), n = 2-6, or -(CH2)-2W(CH2)2- wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or R3Rbaminoxy group, wherein R3Rb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_a$ , n = 2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_3)alkyl$ [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C2)alkvl]. O or S; (C1-C3)alkylthic group selected from methylthic, ethylthic, propylthic or allylthic; C6-arylthic group selected from phenylthio or substituted phenylthio (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino);C<sub>6</sub>-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_5$ -aryl; substituted  $C_5$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihab( $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_3)$ -alkyl, amino or carboxy);  $(C_2-C_3)$ -aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; hydroxy group; a-hydroxy(Cl-C<sub>2</sub>)alkyl group selected from hydroxymethyl, a-hydroxyethyl or a-hydroxyrt-methylethyl or a-hydroxyrtopyl; halo-(G-C<sub>2</sub>)alkyl group; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, tifluoroacetyl, (C<sub>2</sub>-C<sub>2</sub>)cycloalkylcarbonyl, (C<sub>2</sub>-C<sub>10</sub>)aroyl selected from benzoyl or naphthoyl, halo substituted (C<sub>2</sub>-C<sub>10</sub>)aroyl, (G-C<sub>10</sub>)alkylbenzoyl, or (heterocycle)-carbonyl, the heterocycles selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom gotionally hawing a benzo or pyrido rind fused thereto:

Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched ( $C_1$ - $C_1$ )alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo ( $C_1$ - $C_4$ )alkoxy, trihalo( $C_1$ - $C_5$ )alkyl, nitro, amino, cyano, ( $C_1$ - $C_4$ )alkoxycarbonyl, ( $C_1$ - $C_4$ )alkylamino or carboxy); ( $C_7$ - $C_6$ )aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl or phenylorpyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C1-c1,a)koxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, embroxycarbonylamino, or propoxycarbonylamino;

and when  $R = R^4(CH_2)_nSO_2$  and n = 0,

R<sup>e</sup> is selected from amino; monosubstituted amino selected from straight or branched (G;-G<sub>2</sub>), adilylamino, cyclopropylamino, evclobtylamino, benzylamino or phenylamino, disubstituted amino selected from dimethylamino, diethylamino, ethyl(I-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, I-mindazolyl, 1-pyrrolyl, 1-(I-Q,3-triazoly) or 4-(1,2-triazoly)l; straight or branched (Gr-G<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or I-methylethyl; (G;-G<sub>2</sub>)aryl group selected from phonyl, a-naphthyl or β-naphthyl; substituted (G;-G<sub>1</sub>)aryl group (substitution selected from halo (G;-G<sub>2</sub>)alkoyyardhonyl, (G;-G<sub>2</sub>)-alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or S heterochom optionally having a bearso or pyridid ring lysed thereto:

Z = N. O. S or Se .

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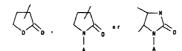
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or } Se$  .

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihado $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxy, substitution or carboxyl;  $(C_7-C_9)$ -aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; and when R = R\*(CH2),SO<sub>2</sub>- and n = 1-4,

and minn in The (Crip. 2002; and In 1 - In, 1994). The selected from straight or branched (Cr-Cyalkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino, disubstituted amino selected from odmethylamino, diethylamino, ethyl(I-methylethylamino, monomethylbenzylamino, piperdinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-1,1,2-3-trazolyl) or 4-(1,2-4-trazolyl); straight or branched (Cr-Cyalkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; RPR-amino(Cr-Cyalkyl group, wherein RPR's is a straight or branched (Gr-Cyalkyl selected from methyl, ethyl, n-propyl or 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPR's is (Ctb<sub>2</sub>), n=2-8, or (Ctb<sub>2</sub>) W(Cb<sub>2</sub>), wherein W is selected from MCC, Cyalkyl (Straight or branched), N-H, N-OB (B is selected from

hydrogen or (C<sub>1</sub>-C<sub>2</sub>)alkyl], O or S; or R\*R\*aminoxy group, wherein R\*R\* is a straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R\*R\* is (CH<sub>2</sub>)<sub>m</sub>, n=2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched]. -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], 0 or S;

 $R^5$  is selected from hydrogen; straight or branched  $(C_1-C_3)$ alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;  $(C_5-C_3)$ arry group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl;  $(C_5-C_3)$ -aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom cottonally having a benzo or printed ring fused thereto:

Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alky;  $C_4$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo( $C_1-C_4$ )alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxy-carbonyl,  $(C_1-C_2)$ alkylamino or carboxy);  $(C_2-C_2)$ -aralkyl group selected from benzyl, 1-phenylethyl. 2-phenylethyl -phenylytoxyl-2-phenylethyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenyloxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenylytoxyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-2-phenyl-

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or (CHs),CODR/where n = 0-4 and R<sup>2</sup> is selected from hydrogen; straight or branched (Ci--Qis)kyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (Ci--Qis)kyl group selected from phonyl, anaphthyl; R<sup>2</sup> is selected from hydrogen; straight or branched (Ci--Ci-)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (Ci--Qis)kyl group selected from phenyl, anaphthyl or β-naphthyl; (Ci--Qis)kyl group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring lused theretox.

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Z = N. O. S or Se .

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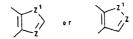
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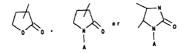
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a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen, straight or branched ( $C_1$ - $C_4$ )alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1$ - $C_4$ )alkovy, trithalo, $(C_1$ - $C_3$ )alkyl, nitro, amino, cyano, ( $C_1$ - $C_4$ )-alkovycarbonyl, ( $C_1$ - $C_2$ )alkylamino or carboxy); ( $C_2$ - $C_6$ )aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or SS heteroatoms and an adjacent appended O heteroatom; or (CH<sub>2</sub>)<sub>0</sub>COOR<sup>7</sup> where n = 0-4 and R<sup>7</sup> is selected from hydrogen; straight or branched (G<sub>1</sub>-C<sub>2</sub>)<sub>a</sub>lkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (G<sub>2</sub>-C<sub>12</sub>)<sub>a</sub>lyl selected from phenyl, α-naphthyl or β-naphthyl; with the provisor that R<sup>2</sup> and R<sup>2</sup> cannot both be hydrogen;

or R<sup>S</sup> and R<sup>S</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>3</sub>, and n = 0-1, -NH, -NG, -G<sub>3</sub> lakoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

 The compound according to Claim 1, wherein: X is selected from amino, NR¹R², or halogen; the halogen is selected from bromine, chlorine, fluorine or iodine; and when X = NR¹R² and R¹ = hydrogen.

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R<sup>1</sup> = methyl or ethyl.

R<sup>2</sup> = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

R is selected from R\*(Grb<sub>a</sub>),CO- or R\*(Grb<sub>a</sub>),SO<sub>2</sub>: and when R = R\*(Grb<sub>a</sub>),CO- and n = 0, R\* is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (Cr-C<sub>2</sub>)alkylamino, cycloptorylamino, cycloptylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(r-methylethylamino, monomethylbenzylamino, pipordinly, norpholinyl, 1-indiazebly, 1-gryrolyl, 1-f(1,2-friazebly) or 4-f(1,2-friazebly) straight or branched (Cr-C<sub>2</sub>)alkyl group selected from methyl or ethyl; (Cr-C<sub>1</sub>)alyl group selected from phenyl, anaphthyl or #naphthyl; substituted (Cr-C<sub>1</sub>)alyl group (substitution selected from tholo, (Cr-C<sub>1</sub>)alkylamino or carboxyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl, nitro, amino, cyano, (Cr-C<sub>1</sub>)alkylamino or carboxyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl, nitro, amino, cyano, (Cr-C<sub>1</sub>)alkylamino or carboxyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl, nitro, amino, cyano, (Cr-C<sub>1</sub>)alkylamino or carboxyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkoxy, carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkyl; nitro, amino, cyano, (Cr-C<sub>1</sub>)alkyl; carboxy-inthalo(Cr-C<sub>1</sub>)alkoxy, carboxy-inthalo(Cr-C<sub>1</sub>)alk

(G2-G2,alkylamino group selected from aminoacetic acid, a-aminoburyirc acid or a-aminopropionicacid and their optical isomers; a-hydroxy(G-G2)alkyl group selected from hydroxymethyl, a-hydroxysthyl or a-hydroxy-1-methyl- ethyl or a-hydroxypropyl; halo(G1-G2)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se.

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or } Se.$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(G_1-G_4)$ alkoxy, trihalo, $(G_1-G_2)$ alkyl, nitro, amino, cyano,  $(G_1-G_4)$ -alkoxycarbonyl,  $(G_1-G_2)$ alkylarmino or carboxy);  $(C_2-C_2)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylorpoyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (G,-C,-Jalkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl; straight or branched butoxycarbonyl or allyloxycarbonyl; straight or branched butoxycarbonyl or allyloxycarbonyl; straight or branched butoxycarbonyl or allyloxycarbonyl; straight or substituted vinyl group (substitution selected from (C,-C,-G,-C,-C,-G,-L)) and (G,-C,-G,-C,-G,-L), (G,-C,-G,-L), (G,-C,-G,-G,-L), halo(C,-C,-G,-L), halo(C,-G,-L), halo(C,-

Z = N, O, S or Se ];

 $(C_1\text{-}C_4)$ alkoxy group;  $C_6\text{-}$ aryloxy group selected from phenoxy or substituted phenoxy (substitution

selected from halo, (c)--C<sub>1</sub>alkyl, nitro, cyano, thiol, amino, carboxy, dl(c)--C<sub>2</sub>)alkylaminoj; (c)--C<sub>1</sub>--C<sub>2</sub>, alkylaminoj; (c)--C<sub>1</sub>--C<sub>2</sub>, alkylaminoj; (c)--C<sub>1</sub>--C<sub>2</sub>, alkylaminoj; (c)--C<sub>2</sub>--C<sub>2</sub>, alkylaminoj; (c)--C<sub>3</sub>--C<sub>4</sub>, alkylaminoj; (c)--C<sub>4</sub>--C<sub>4</sub>, alkylaminoj; (c)--C<sub>4</sub>--C<sub>4</sub>, alkylaminoj; (c)--C<sub>4</sub>--C<sub>4</sub>, alkylaminoj; (c)--C<sub>4</sub>--C<sub>4</sub>, alkylaminoj; (c)--C<sub>4</sub>--C<sub>4</sub>, alkylaminoj; (c)--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>--C<sub>4</sub>-

R<sup>1</sup> is selected from hydrogeni (G--C<sub>2</sub>)alkyl group selected from mothyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylethyl, n-butyl, 1-methylopolyl or 2-methylpropyl is -methylopolyl or straight or branched (C--C<sub>2</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino, disubstituted amino selected from dimethylamino, diethylamino, benzylamino, piografinyl, mepholinyl, 1-miralogyl, 1-pyroyly, 1-(1,2.3-tiazelyl) or 4-(1,2.4-tiazolyl); (C<sub>2</sub>-C<sub>1</sub>)alyni) group selected from phenyl, a-naphthyl or β-naphthyl; substituted (G<sub>2</sub>-C<sub>1</sub>)alkyl group selected from phenyl, a-naphthyl or β-naphthyl; substituted (G<sub>2</sub>-C<sub>1</sub>)alkyl group selected from halo, (C--C<sub>2</sub>)alkyl, almon, amino, cyano, (C--C<sub>2</sub>)alkyl, propionyl, chloroacelyl, inchloroacelyl, (C<sub>3</sub>-C<sub>2</sub>)cycloakylcarbonyl, (C<sub>4</sub>-C<sub>3</sub>)argyl selected from benzoyl or naphthoyl, halo substituted (C<sub>2</sub>-C<sub>1</sub>)argyl, (C<sub>1</sub>-C<sub>2</sub>)alkyllenzoyl, or (heterocycle)solected from a five membered aromatic or saturated ring with one N, O, S or Se heteroaction optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se.

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a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -

alkoxycarbonyl,  $(C_1-C_3)$ alkylamino or carboxy);  $(C_7-C_9)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

and when  $R = R^4 (CH_2)_n SO_2$ - and n = 0,

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R<sup>4</sup> is selected from amino; monosubstituted amino selected from straight or branched (c<sub>1</sub>-c<sub>2</sub>)aklylamino, cyclopropylamino, bezolamino or phenylamino; disubstituted amino selected from dimetrylamino, diethylamino, ethyl(1-metrylethyllamino, monometrylebnoylamino, piperdinyl, morpholinyl, 1-imidazobyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2-t-triazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from metrilyl or ethyl; (C<sub>6</sub>-C<sub>1</sub>)aryl group selected from phenyl, anaphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>1</sub>)alkyl group (substitution selected from halo, (C<sub>1</sub>-C<sub>1</sub>)alkoyl, withalc(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoylgorphyl, (C<sub>1</sub>-C<sub>2</sub>)alkylgramino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

$$\downarrow$$

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ ,

(A is selected from hydrogen; straight or branched  $(C_1-C_2)alkyl;$   $C_2-aryl;$  substituted  $C_4-aryl$  (substitution selected from halo, $(C_1-C_2)alkxyl;$  nitro, amino, cyano,  $(C_1-C_2)alkxyl$  nitro, amino, cyano,  $(C_1-C_2)alxyl$  group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylothyyl, 2-phenylethyl or phenylothyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; and when R = Rf (CH<sub>2</sub>)<sub>2</sub>SO<sub>2</sub>- and n = 1-4,

R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl; R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; (C<sub>2</sub>-C<sub>1</sub>)alayl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>1</sub>-C<sub>2</sub>)aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benze or pyrido ring fused therefore.

Z = N. O. S or Se .

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or } Se$  ,

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

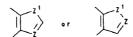
(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₄-aryl; substituted C₄-aryl (substitution selected from halo.(C₁-C₄)alkovy, trihalo(C₁-C₄)alkyl, nitro, amino, cyano, (C₁-C₄)alkovycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₂-C₃)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or So heteroatoms, or a six membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom; or  $-(Clt_2),COOR^*$  where n=0-4 and  $R^*$  is selected from hydrogen; straight or branched  $(C_1-C_2)$ alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(C_0-C_1)$ aryl group selected from phenyl, a-naphthyl or A-naphthyl or

R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C<sub>5</sub>-C<sub>1</sub>-)ayn'l group selected from phenyl, --naphthyl or β-naphthyl; (C<sub>7</sub>-C<sub>5</sub>)-aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

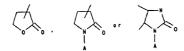
Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



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(A is selected from hydrogen; straight or branched ( $C_1$ - $C_1$ )alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo,( $C_1$ - $C_2$ )alkoy, trihalo( $C_1$ - $C_2$ )alkyl, nitro, amino, cyano, ( $C_1$ - $C_3$ )alkoxycarbonyl, ( $C_1$ - $C_3$ )alkylamino or carboxy); ( $C_7$ - $C_9$ )aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or  $(CH_2)_0COOR^{2}$  where n=0-4 and  $R^2$  is selected from hydrogen; straight or branched  $(Ch-C_2)alkyl$  selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(C_0-C_1)ayl$  selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl with the provise that  $R^2$  and  $R^2$  cannot both be hydrogen;

or R<sup>5</sup> and R<sup>6</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>3</sub> and n = 0-1, -NH, -N(G-C<sub>2</sub>)<sub>4</sub>kloxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

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- The compound according to Claim 1, wherein: X is selected from amino, NR'R<sup>2</sup>, or halogen; the halogen is selected from bromine, chlorine, fluorine or iodine; and when X = NR'R<sup>2</sup> and R! = methyl or ethyl.
- and when X = NR'R' and R' = methyl or eth $R^2 = methyl or ethyl.$

R is selected from  $R^4$  (CH<sub>2</sub>)<sub>n</sub>CO- or  $R^4$  (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-; and when  $R = R^4$  (CH<sub>2</sub>)<sub>n</sub>CO- and n = 0,

R<sup>1</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or shryl; (C<sub>4</sub>-C<sub>1</sub>-layr) group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>4</sub>-C<sub>1</sub>-layr) group (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>-)alkoxy, nitro, amino, or (C<sub>2</sub>-C<sub>2</sub>-)alkoxycarboxyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom sotionally harbyna benzo or yvrido rind fused thereto:



Z = N, O or S

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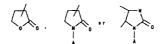
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or a five membered aromatic ring with two N, O, or S heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z = N. O or S.

or a five membered saturated ring with one or two N, O or S heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C1-C2)alkyl; C5-aryl)

(G:-C-)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, straight or substituted vinyl group, [substitution selected from from (G:-C<sub>2</sub>)alkyl group, (G:-C<sub>3</sub>)alkyl group, (G:-C<sub>3</sub>)alkyl group, (G:-C<sub>3</sub>)alkyl group, (G:-C<sub>3</sub>)alkyl group), (G:-C<sub>3</sub>)alkyl), (G:

R4 is selected from hydrogen; (C1-C2)alkyl group selected from methyl or ethyl; amino; monosubstituted amino selected from straight or branched (C1-C6)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl or 1-(1,2,3-triazolyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or βnaphthyl; substituted (C6-C10)aryl group, (substitution selected from halo, (C1-C4)alkoxy, nitro, amino, (C1-C4)alkoxycarbonyl); acyloxy or haloacyloxy group selected from acetyl, propionyl or chloroacetyl; (C1-C4)alkoxy group; RaRbamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n = 2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_3)$ alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2W-(CH2)2wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; halo (C<sub>1</sub>-C<sub>3</sub>)alkyl group; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or

propoxycarbonylamino;

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and when  $R = R^4 (CH_2)_n SO_2$  and n = 0,

R<sup>e'</sup> is selected from straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl, group selected from methyl or ethyl; (C<sub>2</sub>-C<sub>3</sub>)ayryl group selected from phenyl, o-naphthyl or β-naphthyl; substituted (C<sub>2</sub>-C<sub>13</sub>)ayrl group, (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, nitro, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, or S heteroatom optionally having a benzo or pyrido ring tused thereto:

Z = N. O or S.

or a five membered aromatic ring with two N, O, or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O \text{ or } S$ :

and when  $R = R^4 (CH_2)_n SO_2$  and n = 1-4,

 $R^{\sigma}$  is selected from hydrogen, straight or branched  $(C_1-C_2)$ alkyl group selected from methyl or ethyl;  $R^{\sigma}$  is selected from hydrogen; straight or branched  $(C_1-C_2)$ alkyl group selected from methyl, ethyl, n-propul or 1-methylalhyl;

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R<sup>5</sup> and R<sup>6</sup> cannot both be hydrogen;

or R<sup>2</sup> and R<sup>2</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>3</sub> and n = 0-1, -NH, -N(G-C<sub>2</sub>)alkoy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethy(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complayes.

40 6. A compound of the formula:

wherein:

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Y is NO<sub>2</sub>;

R is selected from  $R^4(CH_2)_nCO$ - or  $R^4(CH_2)_nSO_2$ -; and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R<sup>4</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>5</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C1-C4)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; (C3-C6)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>5</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or βnaphthyl; substituted (C6-C10)aryl group (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; α-amino(C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from aminomethyl,  $\alpha$ -aminoethyl,  $\alpha$ -aminopropyl or  $\alpha$ -aminobutyl; carboxy(C<sub>2</sub>-C<sub>4</sub>)alkylamino group selected from aminoacetic acid, a-aminobutyric acid or a-aminopropionic acid and their optical isomers; (C7-C3)aralkylamino group; (C1-C4)alkoxycarbonylamino substituted (C1-C4)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; α-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, α-hydroxyethyl or α-hydroxy-1-methylethyl or α-hydroxypropyl; α-mercapto(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from mercaptomethyl,  $\alpha$ -mercaptoethyl,  $\alpha$ -mercapto-1-methylethyl or  $\alpha$ -mercaptopropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substituted from halo, $(C_1-C_4)$ alkoxy, trihalo( $(C_1-C_2)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_2)$ alkylamino or carboxy);  $(C_7-C_2)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, tifluoroacetyl, (C<sub>1</sub>-C<sub>2</sub>)-cycloalky/carbonyl, (C<sub>2</sub>-C<sub>1</sub>)aroyl selected from benzoyl or naphthoyl, halo substituted (C<sub>2</sub>-C<sub>1</sub>)aroyl, (C<sub>1</sub>-C<sub>2</sub>)alvoyl, the heterocycles selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

10 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkovy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkovycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or otherwloroovl)

Z = N, O, S or Se;

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(C;-C,alkovy group; Č;-arylovy group selected from phenovy or substituted phenoxy (substitution selected from halo, (C;-C,a)alkyl, nitro, cyano, thiol, amino, carboxy, di(C;-C<sub>3</sub>)alkylamino); (C;-C<sub>1</sub>)a-aralkylovy group; (ivhyloxy or substituted vinyloxy group (substitution selected from (G;-C<sub>4</sub>)alkyl, cyano, carboxy, or (C;-C<sub>1</sub>)ayryl selected from phenyl, e-naphthyl or β-naphthyl); PtPamino(G;-C<sub>4</sub>)alkyl, cyano, group, wherein PtPa is a straight or branched (C;-C<sub>4</sub>)alkyl selected from methyl, ethyl, n-pcyl, 1-methylethyl, n-butyl, 1-methylgropyl, 2-methylpropyl or 1,1-dimethylethyl or PtPa is (Ct+<sub>3</sub>)<sub>m</sub>, n=2-6, or (Ct+<sub>3</sub>)<sub>m</sub>(Ct+<sub>3</sub>)<sub>m</sub> wherein N NoB (B is selected from hydrogen or (C;-C<sub>3</sub>)alkyl), O or S; or PtPaminoxy group, wherein PtPa is a straight or branched (C;-C<sub>3</sub>)alkyl selected from methyl, ethyl, n-pcopyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methin Vis selected from +(C;-C<sub>3</sub>)alkyl], O or S; or PtPaminoxy group, wherein PtPa is a straight or branched (C;-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C;-C<sub>3</sub>)alkyl], O or S; or S;

and when  $R = R^4(CH_2)_aCO$ - and n = 1-4.

R<sup>1</sup> is selected from hydrogen; amino; straight or branched (C<sub>1</sub>-C<sub>2</sub>)akylv group selected from methyl, ethyl, n-methyl-liny, n-butyl, 1-methyl-liny(; (c<sub>2</sub>-C<sub>2</sub>)-cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclobxyl; substituted (C<sub>2</sub>-C<sub>2</sub>)-cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclobxyl; group cycloalkyl; group (substitution selected from high (n-C<sub>2</sub>)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>2</sub>)alcyly; (C<sub>2</sub>-C<sub>1</sub>)-cycloalkyl; group (substitution selected from high (n-C<sub>2</sub>)alkylyamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)alkylyamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)alkylyamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)alkylyamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)akylyamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)arkylyamino or carboxy); (C<sub>2</sub>-C<sub>2</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>2</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>2</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>2</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>3</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>3</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>3</sub>)arkylyamino or carboxy); (C<sub>3</sub>-C<sub>3</sub>)arkylyamino or carboxylyamino or carboxy

Z = N, O, S or Se,

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or Se}$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched ( $C_1$ - $C_1$  |alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo,( $G_1$ - $G_2$ ) |alkyl, nitro, amino, cyano, ( $G_1$ - $G_2$ ) alkoxycarbonyl, ( $G_1$ - $G_2$ ) airkylamino or carboxy); ( $G_2$ - $G_2$ ) |aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylorpyly)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two, N, O, S or Se heteroatoms, and an adjacent appended O heteroatom; (C;-C;alkoxy group; C;-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from hale, (C;-C;alkylamino); (C;-C;alkylamino); (C;-C;alkylamino); (C;-C;alkylamino); (C;-C;alkylamino); (C;-C;alkylamino); (C;-arylthio group selected from methylthio, ethylthio, propylthio or allylthio; C;arylthio group selected from phenylthio or substituted phenylthio or substituted phenylthio or substituted phenylthio or substituted phenylthio; (C;-arylthio); (C;-arylthio);

Z = N, O, S or Se

or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto;

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched ( $C_1$ - $C_4$ )alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo,( $C_1$ - $C_4$ )alkoxy, trihalo( $C_1$ - $C_5$ )alkyl, nitro, amino, cyano, ( $C_1$ - $C_4$ )alkoxycarbonyl, ( $C_1$ - $C_4$ )alkylamino or carboxy); ( $C_7$ - $C_5$ )aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylorpyly)

or a six membered aromatic ring with one to three N, Q,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms, and an adjacent appended O heteroatom; hydroxy group; mercapto group; mono- or di-straight or branched chain (Ci-C<sub>c</sub>)alkylamino group selected from methyl, ethyl, n-propy), 1-methylpropy), 2-edimethylpropy), 2-edimethylpropy), 2-edimethylpropy), 3-methylpropy), 3-methylpropy), 1,1-dimethylpropy), 1,1-dimethylpropy), 2-edimethylpropy), 2-edimethylpropy), 3-methylpropy), 3

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

$$\downarrow_{i}^{i}$$
 ..  $\downarrow_{i}^{i}$ 

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_1)aikyl; C_6-aryl;$  substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_2)aikovy,$  trihalo $(C_1-C_3)aikyl,$  nitro, amino, cyano,  $(C_1-C_4)aikovy$ carbonyl,  $(C_1-C_2)aikyl,$  alkovycarbonyl,  $(C_1-C_2)aikyl,$  alkovycarbonyl,  $(C_1-C_2)aikyl,$  arbonylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl or phenylethyl.

or a six membered aromatic ring with one to three N. O. S or Se heteroatoms, or a six membered saturated ring with one or two N. O. S or Se heteroatoms and an adjacent appended O heteroatom: (Ci-Ci-)alkovycarbonylamino group selected from ter-butoxycarbonylamino, allyloxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino; (Ci-Ci-Qialkovycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched butoxycarbonyl; RPR<sup>a</sup>mino(Ci-Ci-Qialkovy group, wherein RPR<sup>b</sup> is a straight or branched (Ci-Ci-Qialkov), ethocycarbonyl; RPR<sup>a</sup>mino(Ci-Ci-Qialkovy, group, wherein RPR<sup>b</sup> is a straight or branched (Ci-Ci-Qialkov), n=2-60, or (Ci-Ci-Qialkov), n=2-60, or (Ci-Ci-Qialkov), Or S; or RPR<sup>a</sup>minoxy group, wherein RPR<sup>b</sup> is a straight or branched (Ci-Ci-Qialkov), n=2-60, or (Ci-Ci-Qialko

## and when $R = R^4(CH_2)_nSO_2$ and n = 0,

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R<sup>4</sup> is selected from amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>2</sub>)-alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-fl,23-triazolyl) or 4-(1,2-4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methyl-propyl, 2-methylpropyl or 1,1-dimethylethyl; (C<sub>2</sub>-C<sub>2</sub>)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopatyl, or cyclohoxyl, substitutiod (C<sub>3</sub>-C<sub>2</sub>-C<sub>2</sub>)cycloalkyl group (substitution selected from phenyl, a-naphthyl or β-naphthyl; substituted (C<sub>3</sub>-C<sub>2</sub>-C<sub>2</sub>)cycloalkyl group; and nino, cyano, (G<sup>-</sup>-C<sub>3</sub>)alkylcymolyl, (G<sup>-</sup>-C<sub>3</sub>)alkylmino or carboxyl; (G<sup>-</sup>-C<sub>3</sub>)arkyl group; halo(G<sup>-</sup>-C<sub>3</sub>)-alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, Q, S or Se heteroctom optionally having a benzo or pyrido ring lysed thereto:

## Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C1-C4)alkyl; C6-aryl; substituted C6-aryl (substitution selected from halo,(C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C9)aralkyl group selected from benzyl, 1phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; RaRbamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH<sub>2</sub>)<sub>a</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>W-(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl],O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1methylpropyl, or 2-methyl- propyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2W(CH2)2- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S:

and when  $R = R^{4}(CH_{2})_{n}SO_{2}$ - and n = 1-4, 35

R4 is selected from hydrogen; straight or branched (C1-C4)alkyl group selected from methyl, ethyl, npropyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; (C1-C4)carboxyalkyl group;  $(C_3-C_6)$ cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C1-C3)alkyl, cyano, amino or (C1-C3)acyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C1-C4)alkoxycarbonyl, (C1-C3)alkylamino or carboxy); (C7-C9)aralkyl group selected from benzyl, 1phenylethyl, 2-phenylethyl or phenylpropyl; (C1-C4)alkoxy group; C6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C1-C3)alkyl,nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); (C<sub>7</sub>-C<sub>10</sub>)aralkyloxy group; RaRbamino(C<sub>1</sub>-C<sub>4</sub>)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2 W(CH2)n- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; or RaRbaminoxy group, wherein RaRb is a straight or branched (C:-Ca)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n=2-6, or -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>- wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; (C1-C3)alkylthio group selected from methylthio, ethylthio or n-propylthio; C6-arylthio group selected from phenylthio or substituted phenylthio (substitution selected from halo, (C1-C3)alkyl, nitro, cyano, thiol, amino, carboxy, di(C1-C3)alkylamino); (C7-C8) aralkylthio group; a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

## Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

#### $Z \text{ or } Z^1 = N. O. S \text{ or } Se$ .

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_4$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_3)$ alkyl, filtro, amino, cyano,  $(C_1-C_4)$ alkoxycarbonyl,  $(C_1-C_3)$ alkylyamino, or carboxy);  $(C_7-C_9)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylptopyl)

or a six membered aromatic ring with one to three N, O,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; hydroxy group, mercapto group; mone or di- straight or branched (C<sub>1</sub>-C<sub>6</sub>)alkylamino group selected from methyl, ethyl, n-propyl, 1-methyletyl, 1-methylpropyl, 2-dimethylbropyl, 2-dimethylbropyl, 2-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl, 3-dimethylbropyl or 1-methyl-tratylpropyl amino; halo(C<sub>1</sub>-C<sub>1</sub>)alkyl group; selected from acetyl, propionyl, chloroacetyl, (C<sub>3</sub>-C<sub>1</sub>)alkyl group; selected from acetyl, propionyl, chloroacetyl, (C<sub>3</sub>-C<sub>1</sub>)alkyl-group; or (heterocycle)achyol, that ostatitude (C<sub>3</sub>-C<sub>1</sub>)aryl, (C<sub>3</sub>-C<sub>1</sub>)alkyl-beropyl, or (heterocycle)achyol, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pryrido rind rivsed thereto:

Z = N, O, S or Se.

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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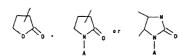
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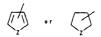
or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₅-aryl; substituted C₅-aryl (substitution selected from haio,(G₁-C₄)alkoya, trihalo(G₁-C₃)alkyl, nitro, amino, cyano, (G₁-G₄)alkoyacarbonyl, (C₁-C₃)alkylamino or carboxy); (C₂-C₃)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylethyl, 2-phenylethyl or phenylethyl.

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (Ct-Cs)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxycarbonyl, allyloxycarbonyl or straight or branched butoxycarbonyl;

 $R^{S}$  is selected from hydrogen; straight or branched ( $C_1-C_2$ )alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; ( $C_2-C_2$ )aryl group selected from phenyl,  $c_1$ -aphthyl or  $\beta$ -naphthyl; ( $C_2-C_2$ )aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent

appended O heteroatom:

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(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_5$ -aryl; substituted  $C_6$ -aryl (substituted from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_2)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_2)$ -alkylamino or carboxy);  $(C_2-C_6)$ -aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or  $-(CH_2)_{n,C}OOR^{n}$  where n = 0.4 and  $R^{n}$  is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ehyl, n-propyl or 1-methylethyl; or  $(C_{k}-C_{10})$ aryl group selected from phenyl, anaphthyl or R-anaphthyl or R-anaphth

 $\mathbb{R}^6$  is selected from hydrogen; straight or branched  $(C_1-C_2)$ alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;  $(C_3-C_3)$ aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl;  $(C_3-C_3)$ -aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



7 = N O S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } S_{\theta}$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C1-C4)alkyl; C6-aryl; substituted C6-aryl

(substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1phenylethyl. 2-phenylethyl or phenylproxyl

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or -(CH<sub>2</sub>),COORT where n = 0-4 and R<sup>2\*</sup> is selected from hydrogen; straight or branched (G)-G<sub>2</sub>)slkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (G<sub>2</sub>-C<sub>1</sub>)slayl selected from phenyl, a-naphthyl or 8-naphthyl, with the proviso that R<sup>2\*</sup> and R<sup>2\*</sup> cannot both be hydrogen;

or R° and R° taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>·, wherein W is selected from (CH<sub>2</sub>)<sub>3</sub> and n = 0-1, -NH, -N(G-C<sub>2</sub>)alk(v) [straight or branched], -N(G-C<sub>2</sub>)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

## 7. The compound according to Claim 6, wherein: Y is NO2:

R is selected from R4(CH2), CO- or R4(CH2), SO2-;

and when  $R = R^{4}(CH_{2})_{n}CO$ - and n = 0.

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R<sup>6</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C1-Cs alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C1-C4)alkyl group selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C3-C6)cycloalkyl group (substitution selected from (C1-C3)alkyl, cyano, amino or (C<sub>1</sub>-C<sub>3</sub>)acyl); (C<sub>6</sub>-C<sub>10</sub>)aryl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (C<sub>6</sub>-C<sub>10</sub>)aryl group (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); α-amino(C<sub>1</sub>-C<sub>4</sub>)alkyl group selected from aminomethyl, α-aminoethyl, α-aminopropyl or α-aminobutyl; carboxy(C2-C4)alkylamino group selected from aminoacetic acid,α-aminobutyric acid or α-aminopropionic acid and their optical isomers; (C<sub>7</sub>-C<sub>9</sub>)aralkylamino group; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino substituted (C<sub>1</sub>-C<sub>4</sub>)alkyl group, substitution selected from phenyl or p-hydroxyphenyl; a-hydroxy(C1-C3)alkyl group selected from hydroxymethyl, a-hydroxyethyl or α-hydroxy-1-methylethyl or α-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

**..** ..

## Z = N, O, S or Se,

or a five membered aromatic ring with two N, O, S or Se hetercatoms optionally having a benzo or pyrido ring fused thereto:

#### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(G<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(G<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (G<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (G<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxyl; (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered atturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, trifluoroacetyl, (C<sub>3</sub>-C<sub>4</sub>)-cycloalkylcarbonyl, (C<sub>6</sub>-C<sub>10</sub>)aroyl selected from benzoyl or naphthoyl, halo substituted (C<sub>6</sub>-C<sub>10</sub>)aroyl, (C<sub>1</sub>-C<sub>4</sub>)alkyloarbozyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se

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ΔN

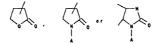
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $(C_1-C_4)$ alkyl;  $C_4$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_4)$ -alkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (G:-G:)alkwy.carbonyl group selected from methoxy.carbonyl, ethoxy.carbonyl, straight or branched

propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl; vinyl or substituted vinyl group isubstitution selected from (G-G-<sub>2</sub>)alkyl group, halogen, (G-G-<sub>1</sub>)aryl group selected from phato, (G-G-G)alkoxy, trihalo(G-G-<sub>2</sub>)alkyl, nitro, amino, cyano, (G-G-<sub>2</sub>)alkyl group, estatitution selected from halo, (G-G<sub>2</sub>)alkyl, nitro, amino, cyano, (G-G-<sub>2</sub>)alkyl group, a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a beargo or pyrido ring fused therefore.

## Z = N. O. S or Se 1:

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(G.-G.)alkov, group: G.-av/loxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, G.-G.-alkylx), nitro, cyano, thiol, amino, carboxy, di(G.-G.)alkylamino); (G.-G.)alkyl, nitro, cyano, thiol, amino, carboxy, of (G.-G.)alkylamino); (G.-G.)alkyl, cyano, carboxy, or (G.-G.)alkyl) selected from phenyl, a-naphthyl or β-naphthyl); R\*R\*amino(G.-G.)alkkyl, cyano, carboxy, or (G.-G.)alkyl) selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R\*R\*B is (G.H.), n=2-6, or -(GH<sub>2</sub>), W(GH<sub>2</sub>); wherein W is selected from McG.-G.)alkyl [straight or branched]. -NH, -NOB [B is selected from hydrogen or (G.-G.)alkyl], O or S: or R\*R\*Parimoxy group, wherein R\*R\*B is a straight or branched (G.-G.)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R\*R\*B is (GH<sub>2</sub>), n=2-8, or -(GH<sub>2</sub>), W(GH<sub>2</sub>); wherein W is selected from -N(G.-G.)alkyl] [straight or branched). -NH, -NOB [B is selected from hydrogen or (G:-G.)alkyl], O or S; and when R = R\*(CH<sub>2</sub>), Octon d n = 1-4.

R¹ is selected from hydrogen; (G.-Cs)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl, aminc; monosubstituted amino selected from straight or branched (G-Cs)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, pipendidnyl, morpholinyl, 1-midacolyl, 1-progrobyl, 1-f(1,2-3-fiazolyl) or 4-f(1,2-4-friazolyl); G-C-c)alkyl group selected from phenyl, α-naphthyl or β-naphthyl; substituted (G.-Cs)alzyl group (substitution selected from halo (G-Cs)alzyl group; (G-Cs)alkyly), artino, artino, cyano, (G-Ca)alkovycarbonyl, (G-Cs)alzylamino or carboxy); acyloxy or haloacyloxy group selected from acetyl, propionyl, chloroacetyl, frichloroacetyl, (G-Cs)alkylybenzoyl, or (heterocycle)selected from benzoyl or naphthyl, halo substituted (G-Cs)aroyl, (G-C-Ca)alkylbenzoyl, or (heterocycle)selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



#### Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C₁-C₂)alkyl; C₂-aryl; substituted C₂-aryl (substitution selected from halo.(C₁-C₂)alkoy, trihalo(C₁-C₂)alkyl, nitro, amino, cyano, (C₁-C₂)alkoyarionyl, (C₁-C₂)alkylamino or carboxyl; (C₂-C₂)aralkyl group selected from benzyl, 1-phonylethyl, 2-phenylethyl or phenylcroyyl)

or a six membered aromatic ring with one to three N. O. S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C<sub>1</sub>-C<sub>4</sub>)alkoxy group; RaRbamino(C<sub>1</sub>-C<sub>4</sub>)alkoxy group, wherein RaRb is a straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^aR^b$  is  $(CH_2)_n$ , n=2-6, or  $-(CH_2)_2W(CH_2)_2$ - wherein W is selected from  $-N(C_1-C_3)$ alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; or R<sup>a</sup>R<sup>b</sup>aminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH<sub>2</sub>)<sub>n</sub>, n = 2-6, or -(CH<sub>2</sub>)<sub>2</sub>-W-(CH<sub>2</sub>)<sub>2</sub>wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl],O or S; C6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); (C1-C3)alkylthio group selected from methylthio, ethylthio, propylthio or allylthio; C6-arylthio group selected from phenylthic or substituted phenylthic (substitution selected from halo, (C1-C4)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>2</sub>)alkylamino); C<sub>6</sub>-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (C1-C4)alkoxy, trihalo(C1-C3)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



## Z = N, O, S or Se

or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido fused thereto:

### $Z \text{ or } Z^1 = N. O. S \text{ or } Se$ .

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alklyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alklyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoyycarbonyl, (C<sub>1</sub>-C<sub>9</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>9</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylgropyl)

or a six membered aromatic ring with one to three N, O,S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; hydroxy group; a-hydroxy(G-C-3)alkyl group selected from hydroxy-t-methylethyl or a-hydroxypropyl; halo (G-C<sub>3</sub>)alkyl group; acyl or haloacyl group selected from acetyl, propionyl, chloracetyl, fitting-cacetyl, (G-C<sub>3</sub>)alkyl group; acyl or haloacyl group selected from benzoyl or naphthoyl, halo substituted (C<sub>4</sub>-C<sub>1</sub>)aroyl, (C<sub>1</sub>-C<sub>3</sub>)alkylbenzoyl,or (heterocycle)carboryl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or syrido ring fused thereto:

Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z or Z¹ ≃ N. O. S or Se .

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoyy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoyycarbonyl. (C<sub>1</sub>-C<sub>3</sub>)alkylyamino or carboxy); (C<sub>7</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl. 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered

saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; (C;-C,)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino; and when  $R = R^*(CH_b, SO_2-$  and n = 0.

Fi<sup>o</sup> is selected from armino; monosubstituted amino selected from straight or branched (G,-C<sub>6</sub>)-alkylamino, cyclopropylamino, cyclobulylamino, benzylamino or phenylamino, disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylsthylamino, monomethylbenzylamino, piperidinyl, mepholinyl, 1-imidazolyl, 1-pyrolyl, 1-(1,2.3-tinazolyl) or 4-(1,2.4-tinazolyl); straight or branched (G-c)alkyl group selected from methyl, ethyl, n-propyl or 1-methylentyl; (G-c-O)aryl group selected from phenyl, e-naphthyl or β-naphthyl; substituted (G<sub>2</sub>-G-)aryl group (substitution selected from halo, (G,-C<sub>3</sub>)akyy, thindo(G,-C<sub>3</sub>)akyy, (G,-C<sub>3</sub>)-alkyyamino or carboxy); a hestrocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido fing fused thereto:

Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>4</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoxy-carbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl or phenylethyl).

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; and when  $R = R^T(Ct_{S_1}, SO_2$ - and n = 1.4.

R<sup>e</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (Ct-C<sub>2</sub>lalkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methyliethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2.3-triazolyl) or 4-(1,2.4-triazolyl); straight or branched (Ct-C<sub>2</sub>)alyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (c4-Ct<sub>2</sub>)aryl group selected from phenyl, anaphthyl or β-naphthyl; substituted (Cc-C<sub>2</sub>)alyl group (substitution selected

from halo,  $(C_1-C_4)$ alkoxy, trihalo $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ alkoxycarbonyl,  $(C_1-C_3)$ -alkylamino or carboxyl;  $(C_1-C_4)$ alkoxy group;  $(C_2-\alpha_1)$ -alkylamino or carboxyl;  $(C_1-C_4)$ -alkyl, nitro cyano, thiol, amino, carboxy, di $(C_1-C_3)$ -alkylamino);  $(C_2-C_1)$ -aralkyloxy group;  $(C_1-C_4)$ -carboxyalkyl group;

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; (C<sub>2</sub>-C<sub>2</sub>)alkyl group selected from phenyl, α-naphthyl or β-naphthyl; (C<sub>2</sub>-C<sub>2</sub>)aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or ovidio ring fused thereto:

Z = N. O. S or Se.

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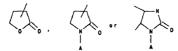
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>4</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)

alkoxycarhonyl. (C;-C;)alkylamino or carboxy); (C;-C;)aralkyl group selected from benzyl, 1phenylethyl, 2-phenylethyl or phenylpropyl) or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or -(CH;),COOR\* where n = 0-4 and R\* is selected from hydrogen; straight or branched (C;-C;)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; of (C;-C;)alkyl group selected from phenyl, a-

naphthyl or  $\delta$ -naphthyl;  $R^*$  is selected from hydrogen; straight or branched ( $C_1$ - $C_2$ )alkyl group selected from methyl, othyl, n-propyl or 1-mothylethyl; ( $C_2$ - $C_3$ )aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl; ( $C_2$ - $C_3$ )aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or S beteroation optionally having a benze or pyrido ring fused theroit.

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Z = N, O, S or Se ,

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N. O. S \text{ or } Se$ .

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

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(A is selected from hydrogen; straight or branched ( $C_1$ - $C_1$  lalkyl;  $C_2$ - $\alpha$ ryl; substituted  $C_6$ - $\alpha$ ryl (substitution selected from halo,( $G_1$ - $G_2$  lalkoxy, trihalo( $G_1$ - $G_2$ ) lalkyl, nitro, amino, cyano, ( $G_1$ - $G_2$ ) alkoxycarbonyl, ( $G_1$ - $G_2$ ) alkyl amino or carboxyl; ( $G_2$ - $G_2$ ) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl  $G_1$ - $G_2$ - $G_3$ - $G_4$ -

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered structed ring with one or two N, O, S or Se heteroatoms and analgacent appended O heteroatom; or (CH<sub>2</sub>),COOR" where n =0.4 and R<sup>2</sup> is selected from hydrogen; straight or branched (G, C<sub>2</sub>)al(N) selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C<sub>2</sub>-C<sub>2</sub>)aryl selected from phenyl, a-naphthyl or 8-naphthyl; with the proviso that R<sup>2</sup> and R<sup>2</sup> cannot both be hydrogen.

or R<sup>3</sup> and R<sup>3</sup> taken together are -{CH<sub>2</sub>}<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n=0-1, -NH, -N(G-C<sub>2</sub>)alkoy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine, and the pharmacologically acceptable organic and inorganic salls or metal complexes.

45 8. The compound according to Claim 6, wherein: Y is NO<sub>2</sub>; R is selected from R<sup>4</sup>(CH<sub>2</sub>)<sub>n</sub>CO- or R<sup>4</sup>(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-;

and when R = Rt (CH2), CO- and n = 0,

R¹ is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (C<sub>1</sub>-c)latilylamino, cycloproyplamino, cycloproyplamino, cherolatinino or phenylamino; disubstituted amino selected from dimethylamino, distribution, selected from dimethylamino, distribution, selected from dimethylamino, distribution, piparidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ehyl, n-pyropyl or 1-methylethyl; (C<sub>2</sub>-C<sub>2</sub>)cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; substituted (C<sub>2</sub>-C<sub>2</sub>)cycly; (C<sub>2</sub>-C<sub>2</sub>-c<sub>1</sub>)cycly group selected from phonyl, a-naphthyl or β-naphthyl; substituted (C<sub>2</sub>-C<sub>2</sub>)alyl group (substitution selected from hato(C<sub>1</sub>-C<sub>2</sub>)alkyl, intro, amino cyano, (C<sub>1</sub>-C<sub>2</sub>)alkovycarbonyl, (C<sub>2</sub>-C<sub>2</sub>)-alkylamino or carboxyl; a-amino(C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from aminocethyl, a-amino(C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from aminocethyl, a-aminocethyl, a-brough carboxycarbonyl; acarboxy(C<sub>2</sub>-C<sub>2</sub>)alkylamino group selected from aminocethyl a-aminocethyl, a-brough carboxycarbonyl; acarboxy(C<sub>2</sub>-C<sub>2</sub>)alkylamino group selected from aminocethyl and aminocethyl acarboxy(C<sub>2</sub>-C<sub>2</sub>)alkylamino group selected from aminocethyl acarboxy(C<sub>2</sub>-C<sub>2</sub>-C<sub>2</sub>)alkylamino group selected from aminocethyl acarboxy(C<sub>2</sub>-C<sub>2</sub>-C<sub>2</sub>)alkylamino group selected from aminocethyl

aminobutyric acid or «-aminopropionic acid and their optical isomers; (C<sub>7</sub>-C<sub>9</sub>)aralkylamino group; (C<sub>1</sub>-C<sub>2</sub>)akoycarbonylamino substituted (C<sub>1</sub>-C<sub>2</sub>)alkyl group, substitution selected from phydroxyethyl a-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymtyl, a-hydroxyethyl or «-hydroxyropropyl; halo(C<sub>1</sub>-C<sub>2</sub>)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N. O. S or Se heteroatom optionally having a benzo or pyrido infa (based therefo:

Z = N, O, S or Se

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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoyx, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoyycarbonyl, (C<sub>1</sub>-C<sub>9</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>9</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se beteroatoms, or a six membered saturated ring with one or two N, O, S or Se beteroatoms and an adjacent appended O heteroatom; acyl or haloacyl group selected from acetyl, propionyl, chloroacetyl, tifluoroacetyl,  $(C_3-C_6)$ -cycloakylcarbonyl,  $(C_3-C_6)$ -acyl selected from benzeyl or naphthoyl, halo substituted  $(C_3-C_6)$ -cycloakylcarbonyl, displacetyl, or (heterocycle)carbonyl, the heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused therefor.

## Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

## $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ .

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_5-aryl$ ; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)$ alkoxy, frihalo $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl,  $(C_1-C_3)$ -alkoxycarbo

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatoms, (C--C<sub>2</sub>)alkovycarbonyl group selected from methovycarbonyl, ethovycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl; vinty or substituted vinyl group [substitution selected from henyl, α-naphthyl, β-naphthyl, β-bushtuted (C-C<sub>2</sub>)alkyly group, halogen, (C-C<sub>2</sub>)alkyly, rinto, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoxycarbonyl, (C-C<sub>2</sub>)alkylyninor or carboxyl, halo(C<sub>1</sub>-C<sub>2</sub>)alkylyn group, a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or S e heteroatom optionally having a benzo or pryridor infin bused therefore.

## Z = N. O. S or Se 1:

(C--C<sub>a</sub>)alkoxy group; C<sub>2</sub>-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C<sub>1</sub>-C<sub>a</sub>)alkyl, nitro, cyano, thiol, amino, carboxy, di(C<sub>1</sub>-C<sub>3</sub>)alkylamino); (C<sub>2</sub>-C<sub>1</sub>)alkyl, cyano, carboxy, or (C<sub>2</sub>-C<sub>3</sub>)alkylamino); (C<sub>2</sub>-C<sub>3</sub>)alkyl, cyano, carboxy, or (C<sub>2</sub>-C<sub>3</sub>-C<sub>3</sub>)alkyl selected from phenyl, a-naphthyl or β-naphthyl); RPR<sup>2</sup>amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, cyano, carboxy, or (C<sub>2</sub>-C<sub>3</sub>-C<sub>3</sub>)alkyl); especially considered from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RPR<sup>2</sup> is (Ch<sub>2</sub>)<sub>m</sub>, n=2-6, or -(Ch<sub>2</sub>)<sub>2</sub>)W(Ch<sub>2</sub>)<sub>2</sub>, wherein W is selected from MC<sub>2</sub>-C<sub>2</sub>)alkyl (staight of branched). -NH, -NOB (B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; or RPR<sup>2</sup>minoxy group, wherein RPR<sup>2</sup> is a straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl], or 2-methylpropyl, or RPR<sup>2</sup> is (Ch<sub>2</sub>)<sub>m</sub>, n=2-6, or -(Ch<sub>2</sub>)<sub>2</sub>)W(Ch<sub>2</sub>)<sub>2</sub>. wherein W is selected from MC<sub>1</sub>-C<sub>3</sub>-2)alkyl (Straight or branched). -NH, -NOB (B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; and when R = R<sup>4</sup>(Ch<sub>2</sub>)<sub>2</sub>-CO- and n=1-4.

R¹ is selected from hydrogen; (C;-Cs)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; amino; monosubstituted amino selected from straight or branched (C;-Cs)alkylamino, cyclopropylamino, cyclopropylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-midazolyl, 1-pryor(byl), 1-f(1,23-fiazolyl) or 4-f(1,24-friazolyl); Cc-Cs)alryl group selected from phenyl, a-naphthyl or β-naphthyl; substituted (Cg-Cs)aryl group (substitution selected from hato, (C;-Cs)alkyly-amino or carboxy); acyloxy or haloacyloxy group selected from acetyl, propionyl, chloroacetyl, (fichloroacetyl, (Cg-Cs)alkyly-amino or carboxy); acyloxy or haloacyloxy group selected from acetyl, propionyl, chloroacetyl, (fichloroacetyl, (Cg-Cs)alkyly-lenzoly) or (heterocycle)selected from acetyl or naphthoyl, halo substituted (Cg-Cs)aryl, (G;-Cs)alkyly-lenzoly) or (heterocycle)selected from a tive membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused theretor.

# Z = N, O, S or Se ,

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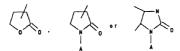
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $(C_1-C_1)alkyl; C_5-aryl;$  substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_4)alkovy,$  trihalo $(C_1-C_3)alkyl$ , nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl.  $(C_1-C_2)aralkyl$  group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyloroyyl)

or a six membered aromatic ring with one to throe N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms, and an adjacent appended O heteroatom; (C;-C;alkovy group; C;-c;aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from hela), (C;-C;alkovy group; C;-c;alkovy, di(C;-C;alkovy), di(C;-C;alkovy), di(C;-C;alkovy), di(C;-C;alkovy), di(C;-c;alkovy), diversing N;-c;alkovy), diversing N;-c;alkovy), diversing N;-c;alkovy, diversing N;-c;alkovy), diversing N;-c;alkovy, diversing N;-c;alkovy), diversing N

group selected from methyllhic, ethyllhic, propyllhic or allylthic, C<sub>2</sub>-aryllhic group selected from henyllhic or substituted phenylthic (substitution selected from halo, (Ci-C<sub>4</sub>)alkyl, nitro, cyano, thicl, amino, carboxy, di(Ci-C<sub>2</sub>)alkylamino); C<sub>2</sub>-arylsulfonyl group selected from phenylsulfonyl or substituted phenylsulfonyl (substitution selected from halo, (Ci-C<sub>4</sub>)alkoxy, trihalo(Ci-C<sub>2</sub>)alkyl, nitro, amino, cyano, (Ci-C<sub>4</sub>)alkoxyarbornyl, (Ci-C<sub>2</sub>)alkoxyarbornyl, (Ci-C<sub>2</sub>)alkoxyarbo

Z = N, O, S or Se,

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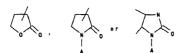
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or a five membered aromatic ring with two N, O,S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(G<sub>1</sub>-C<sub>4</sub>)alkoy, trihalo(G<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (G<sub>1</sub>-C<sub>4</sub>)alkyaryarino or carboxyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, 0.5 or Se heteroatoms, or a six membered saturated ring with one or two N, 0.5 or Se heteroatoms and an adjacent appended O heteroatom; hydroxy group;  $\alpha$ -hydroxy(0- $C_0$ -lalky) group selected from hydroxymethyl,  $\alpha$ -hydroxyethyl or  $\alpha$ -hydroxyethyl or  $\alpha$ -hydroxyethyl or  $\alpha$ -hydroxyethyl,  $(C_0$ - $C_0$ -s)aklyl group; aeyl or haleacyl group selected from acetyl, propionly, chiloroacelyl, triflutoroacelyl,  $(C_0$ - $C_0$ -s)aklylselycarbonyl,  $(C_0$ - $C_0$ -p)aroly selected from benzoyl or naphthoyl, halo substituted  $(C_0$ - $C_0$ - $C_0$ -p)aryl,  $(C_0$ - $C_0$ -p)aroly selected from benzoyl or naphthoyl. halo substituted  $(C_0$ - $C_0$ - $C_0$ -p)aroly selected from  $C_0$ -point  $C_0$ -po

## Z = N, O, S or Se .

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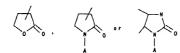
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



- (A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₄-aryl; substituted C₄-aryl (substitution selected from halo,(C₁-C₄)alkoy, trihaio(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)alkoyarbonyl, (C₁-C₃)alkylamino or carboxyl; (C₂-C₃)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl c₁-phenylethyl c₁-phenylethyl c₂-phenylethyl c₂-phenyle
- or a six membered aromatic ring with one to three N, O, S or So heteroatoms, or a six membered saturated ring with one or two N, O, S or So heteroatoms and an adjacent appended O heteroatom; (C1-C1) plakoxycarbonylaminio group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino; allyloxycarbonylamino and when R = Rf (C1e), 2O2 and n = 0,
  - R<sup>4</sup> is selected from arrino; monosubstituted amino selected from straight or branched (c;-C<sub>2</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; stabustituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-1,(2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (C;-C<sub>2</sub>)alkyly group selected from methyl, ethyl, n-propyl or 1-methylethyl; (c;-C<sub>2</sub>)-apryl group (substitution selected from halo (C;-C<sub>2</sub>)alkoly, group selected from discovery (c;-C<sub>2</sub>)-paryl group (substitution selected from halo (C;-C<sub>2</sub>)alkoly, straiba(C;-C<sub>2</sub>)alkyl, intio, amino, cyano, (C;-C<sub>2</sub>)alkovyardhoryl, (c;-C<sub>2</sub>)alkylamino or carboxyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or S elseterostem optionally having a beance or pyridic ring fused thereto:

#### Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

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 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched  $(C_1-C_1)$ alkyl;  $C_6$ -aryl; substituted  $C_6$ -aryl (substitution selected from halo, $(C_1-C_2)$ alkoxy, trihalo( $(C_1-C_3)$ alkyl, nitro, amino, cyano,  $(C_1-C_4)$ -alkoxycarbonyl.  $(C_1-C_3)$ alkyl, amino or carboxy);  $(C_7-C_9)$ aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl, 2-phenylethyl or phenylethyl).

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; and when  $R = R^{*}(CH_{2})SO_{2}$ , and n = 1-4,

R<sup>e</sup> is selected from hydrogen; amino; monosubstituted amino selected from straight or branched (Cr-C<sub>2</sub>) alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dinethylamino, diethylamino, ethyl(t-mothylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pytrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl); straight or branched (Cr-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl, R<sup>\*</sup>PRamino(Gr-C<sub>2</sub>)-alkovy group, wherein R<sup>\*</sup>PR is a straight or branched (Gr-C<sub>2</sub>)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or 1-methyl is Grb, 1-methyl is selected from thydrogen or (Cr-C<sub>2</sub>)alkyl, Selected from thydrogen or (Cr-C<sub>3</sub>)alkyl, Or 8: or R<sup>\*</sup>PRaminoxy group, wherein R<sup>\*</sup>Pi is a straight or branched (Cr-C<sub>3</sub>)alkyl selected from methylpropyl or 2-methylpropyl or 3-methylpropyl, or 2-methylpropyl or 3-methylpropyl or 3

R<sup>5</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (G<sub>2</sub>-C<sub>2</sub>)aprly group selected from phenyl, α-naphthyl or β-naphthyl; (G<sub>2</sub>-C<sub>3</sub>)-aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

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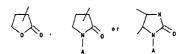
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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched  $\{C_1-C_1\}alkyl; C_5-aryl; substituted <math>C_6$ -aryl (substituted from halo, $\{C_1-C_2\}alkoyx\}$ , trihalo $\{C_1-C_2\}alkyl$ , nitro, amino, cyano,  $\{C_1-C_4\}-alkoyx\}$  and  $\{C_1-C_2\}aralkyl$  group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethyl,

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or  $-(CH_2)_nCOOR'$  where n=0-4 and R' is selected from hydrogen: straight or branched (G-C-ja)likyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(C_0-C_{10})$ aryl group selected from phenyl, anaphthyl or  $\frac{A}{n-n}$ aphthyl; G

R<sup>S</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; (C<sub>4</sub>-C<sub>1</sub>-glaryl group selected from phenyl, a-naphthyl or *8*-naphthyl; (C<sub>7</sub>-C<sub>5</sub>)aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



### Z = N. O. S or Se .

a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

## $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>1</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>1</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-

i or a six membered aromatic ring with one to three N, O, S or Se hetercatoms, or a six membered saturated ring with one or two N, O, S or Se hetercatoms and an adjacent appended O hetercatom; or (CH<sub>2</sub>), COOR<sup>27</sup> where n = 0.4 and R<sup>2</sup> is selected from hydrogen; shaight or branched (C<sub>1</sub>-C<sub>2</sub>)allyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C<sub>4</sub>-C<sub>2</sub>)alryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R<sup>2</sup> and R<sup>2</sup> cannot both be hydrogen.

or R° and R° taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>3</sub> and n = 0-1, -NH.
-N(C<sub>1</sub>-C<sub>2</sub>)alkyl [straight or branched], -N(C<sub>1</sub>-C<sub>2</sub>)alkxxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

The compound according to Claim 6, wherein: Y is NO<sub>2</sub>;
 R is selected from R<sup>4</sup>(CH<sub>2</sub>)<sub>n</sub>CO- or R<sup>4</sup>(CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>-;

phenylethyl, 2-phenylethyl or phenylpropyl)

and when  $R = R^4(CH_2)_nCO$ - and n = 0,

R¹ is selected from hydrogen, amino, monosubstituted amino selected from straight or branched (C<sub>1</sub>-c)alkylamino, cyclopropylamino, cyclopropylamino, cerobautylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-(1,2-3-triazolyl) or 4-(1,2-4-triazolyl), straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl, C<sub>2</sub>-C<sub>3</sub>)alyr group selected from phonyl, anaphthyl or β-naphthyl; substituted (S<sub>2</sub>-C<sub>3</sub>)alyr group (substitution selected from halo, (C<sub>1</sub>-C<sub>3</sub>)alkylamino proup selected from manino, cyano, (C<sub>1</sub>-C<sub>3</sub>)alkylamino, (C<sub>1</sub>-C<sub>3</sub>)alkylamino group selected from aminoacetic acid, a-aminoburyire acid or a-aminopropionicacid and their optical isomers; a-hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl group selected from hydroxymethyl, a-hydroxyethyl or a-hydroxy-1-methylethyl or a-hydroxypropyl; halo(C<sub>1</sub>-C<sub>3</sub>)alkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring lised theretic:

Z = N. O. S or Se .

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50 or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

$$\sum_{i}^{i}$$
 ..  $\sum_{i}^{i}$ 

### $Z \text{ or } Z^1 = N, O, S \text{ or } Se$

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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>5</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, (C<sub>1</sub>-C<sub>5</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heterostoms, or a six membered saturated ring with one or two N, O, S or So heterostoms and an adjacent appended O heterostom; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl group selected from methoxycarbonyl, ethoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, vnyl or substituted vinyl group [substitution selected from (C<sub>1</sub>-C<sub>2</sub>)alkyl group, halogen, (C<sub>2</sub>-C<sub>1</sub>)aryl group selected from phanyl, α-nathtlyl, β-naphthyl, substituted (C<sub>2</sub>-C<sub>1</sub>)alkyl group, substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, thialo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, armino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, chyloxyl, (C<sub>1</sub>-C<sub>2</sub>)alkylyamino or carboxy), halo(C<sub>1</sub>-C<sub>2</sub>)alkyl group, a heterocyto group selected from a five membered aromatic or saturated ring with one N, O, S or Se heterostom optionally having a benzo or privite ring time determined.

### Z = N, O, S or Se;

(c)-C, Jalkovy group; Cs-arylovy group selected from phenoxy or substituted phenoxy (substitution selected from hab. (Cı-C-Q-Ialkyl, nitro. cyano, thiol, amino, carbovy, disc. C-Q-Jalkyl, cyano, carboxy, or (C<sub>1</sub>-C<sub>2</sub>-C<sub>3</sub>-Ialy) selected from phenyl, a-naphthyl or B-naphthyl; R<sup>\*\*</sup>P\*amino(C)-C<sub>3</sub>-Ialkoxy group, wherein R<sup>\*\*</sup>P\* is a straight or branched (Cı-C<sub>3</sub>-Ialkyl selected from methyl, ethyl, n-propyl, 1 methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl or R<sup>\*\*</sup>R\* (CH<sub>2</sub>), n=2-6, or -(CH<sub>2</sub>)xW(CH<sub>2</sub>)z-wherein W is selected from N/G:-C<sub>3</sub>-Ialkyl [statight or branched]. NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>-Ialkyl), O or S; or R<sup>\*\*</sup>R\*Paminoxy group, wherein R<sup>\*\*</sup>B\* is a straight or branched (C<sub>1</sub>-C<sub>4</sub>-Ialkyl selected from methyl, ethyl, n-propyl. 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or R<sup>\*\*</sup>R\* is (CH<sub>2</sub>), n=2-6, or -(CH<sub>2</sub>)xW(CH<sub>2</sub>)z-wherein W is selected from -N(C<sub>1</sub>-C<sub>3</sub>-Ialkyl] [Straight or branched]. NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>2</sub>-Ialkyl], O or S; and when R = R\*\* (CH<sub>2</sub>)xCO and n=1-4.

R¹ is selected from hydrogen (C--C<sub>4</sub>)alkyl group selected from methyl, ehyl, n-propyl. 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; amino, monosubstituted amino selected from straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, elithylamino, ethyl(1-methylethyl)lamino, momethylben-zylamino, piperdinyl, morpholinyl, 1-midazolyl, 1-cyrolyl, 1-t(1,23-triazolyl) or 4/L-4-triazolyl); (C<sub>2</sub>-C<sub>1</sub>-)aryl group selected from phenyl, α-naphthyl or β-naphthyl: substituted (C<sub>2</sub>-C<sub>1</sub>-)aryl group (substituted (C<sub>2</sub>-C<sub>3</sub>-)aryl group selected from halo, (C<sub>1</sub>-C<sub>3</sub>-)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>-)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>3</sub>-)alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>-)alkylamino or carboxy); acyloxy or haloacyloxy group selected from benzoyl or naphthyl, halo substituted (C<sub>2</sub>-C<sub>3</sub>-)aryl, (C<sub>1</sub>-C<sub>3</sub>-)aryl, (C<sub>1</sub>-C<sub>3</sub>-)aryl, or floterocyte)carbonyl, the

heterocycle selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

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a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

(A is selected from hydrogen; straight or branched (C.-C.)alkyl;  $C_c$ -aryl; substituted  $C_c$ -aryl (substitution selected from halo,(G.-C.)alkoxy, trihalo(C1-C.)alkyl, nitro, amino, cyano, (G1-C.)-alkoxycarbonyl, (C1-C.)alkylamino or carboxy); (C7-C.)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatoms (Cj-Cjalkov, group, Phemanino(Cj-Cjalkov, group, wherein RPPs is a straight or branched (Cj-Cjalkov, group, Phemanino(Cj-Cjalkov, group, wherein RPPs is (Alb,), n = 2-8, or (Chb), W(Chb). wherein W is selected from McCj-Cjalkov, Israeling to branched, NH, -NOB [B is selected from hydrogen or (Cj-Cjalkov, lot), n = 2-8, or (-Rb), W(Chb), wherein W is selected from methyl, ethyl, n-propyl, 1-mothylotyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or PhPs is (Chb), n = 2-8, or (-Rb), W(Chb), wherein W is selected from N(Cj-Cjalkov, lot), n = 2-8, or (-Rb), W(Chb), wherein W is selected from N(Cj-Cjalkov, lot), and the selected from hydroxy methyl, a hydroxyethyl or a-hydroxy-1-methylethyl or a-hydroxyethyl or a-hydroxy-1-methylethyl or a-hydroxyethyl proup selected from hydroxy methyl, a hydroxy-1-methylethyl or a-hydroxyethyl propulamino group selected from hydroxyethyl propulamino group selected from hydroxyethyl propulamino group selected from hydroxyethyl propulamino group selected from hydroxyethylmino, allyloxycarbonylamino, methox-ycarbonylamino, ethoxycarbonylamino, ethoxycarbonylamino, methox-ycarbonylamino, ethox-ycarbonylamino, allyloxycarbonylamino, allyloxycarb

and when  $R = R^4$  (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>- and n = 0,

R<sup>e</sup> is selected from amino; monosubstituted amino selected from straight or branched (c<sub>1</sub>-c<sub>2</sub>)-alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethylamino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl, 1-1(1.2-3-triazolyl) or 4-(1.2.4-triazolyl); straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from phenyl, enaphthyl or β-naphthyl; substituted (c<sub>2</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkyoy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyly, nitro, amino, cyano, (C<sub>1</sub>-C<sub>2</sub>)alkyropathonyl, (C<sub>1</sub>-C<sub>2</sub>)alkylyamino or carboxy); a

heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se ,

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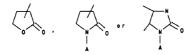
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or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



36 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkowy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>2</sub>-C<sub>3</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; and when  $R = R^{\alpha}(CH_{2},SO_{2})$  and n = 1-4.

 $\mathbf{R}^{\mathbf{f}}$  is selected from hydrogen; straight or branched (Ci-C<sub>2</sub>)alkyl group selected from methyl or eithyl;  $\mathbf{R}^{\mathbf{f}}$  is selected from hydrogen; straight or branched (Ci-C<sub>3</sub>)alkyl group selected from methyl, ethyl, nepropyl or 1-methylethyl; (Ci-C<sub>3</sub>)aryl group selected from phenyl, a-naphthyl; (Ci-C<sub>3</sub>)-aralkyl group; a hoterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N. O. S or Se .

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

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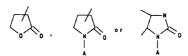
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or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>5</sub>-aryl; substituted C<sub>5</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>3</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>5</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenyloropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or -(CH<sub>2</sub>)<sub>x</sub>COOR<sup>2</sup> where n = 0-4 and R<sup>2</sup> is selected from hydrogen; straight or branched (C<sub>2</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C<sub>4</sub>-C<sub>1</sub>a)aryl group selected from phenyl, anabhthyl or 4-nabhthyl o

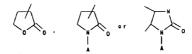
 $R^{\delta}$  is selected from hydrogen; straight or branched ( $C_1$ - $C_9$ )alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; ( $C_8$ - $C_9$ )aryl group selected from phenyl, a-naphthyl or  $\beta$ i-naphthyl; ( $C_7$ - $C_9$ )-aralkyl group; a heterocycle group selected from a five membered aromatic or saturated ring with one N, 0, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O, S \text{ or } Se$ 

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



10 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>4</sub>)alkyl; C<sub>6</sub>-aryl; substituted C<sub>6</sub>-aryl (substitution selected from halo,(C<sub>1</sub>-C<sub>4</sub>)alkoxy, trihalo(C<sub>1</sub>-C<sub>2</sub>)alkyl, nitro, amino, cyano, (C<sub>1</sub>-C<sub>4</sub>)-alkoxycarbonyl, (C<sub>1</sub>-C<sub>3</sub>)alkylamino or carboxy); (C<sub>7</sub>-C<sub>2</sub>)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N, O, S or Se heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or  $(Ct_2)_COOR^{-1}$  where n=0.4 and R<sup>T</sup> is selected from hydrogen; straight or branched  $(Ct_1-C_2)_RCI_1$  selected from methyl, ethyl, n-propyl or 1-methylethyl; or  $(C_c-C_{10})_RV_1$  selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl; with the proviso that R<sup>5</sup> and R<sup>5</sup> cannot both be hydrogen that R<sup>5</sup> and R<sup>5</sup> cannot be R<sup>5</sup> canno

or R<sup>5</sup> and R<sup>6</sup> taken together are -{CH<sub>2</sub>}<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n = 0-1, -NH, -NCG-C<sub>2</sub>)alkyl [straight or branched]. -NCG-C<sub>4</sub>)alkovy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

## 25 10. The compound according to Claim 6, wherein: Y is NO2,

R is selected from R4(CH2), CO- or R4(CH2), SO2-;

and when  $R = R^4 (CH_2)_n CO$ - and n = 0.

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 $R^i$  is selected from hydrogen; straight or branched (C--C<sub>2</sub>)alkyl group selected from methyl or ethyl; (C<sub>8</sub>-C<sub>10</sub>)aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ -naphthyl; substituted (C<sub>8</sub>-C<sub>10</sub>)aryl group (substitution selected from halo, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, nitro, amino, or (C--C<sub>2</sub>)alkoxy,carbonyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom optionally having a benze or pyridor ing (used thereto:

Z = N, O or S

or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

Z = N, O or S,

or a five membered saturated ring with one or two N, O or S heteroatoms and an adjacent appended O heteroatom:

10 (A is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl; C<sub>6</sub>-aryl)

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(Cj-C<sub>4</sub>)alkoxycarbonyl group selected from methoxycarbonyl, straight or branched propoxylcarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, straight or branched butoxycarbonyl or allyloxycarbonyl, straight or substituted vinylorgoup, [substitution selected from [cj-C<sub>2</sub>)alkyl group, halpenyl group selected from phenyl, a-naphthyl, β-naphthyl, substituted (C<sub>2</sub>-C<sub>12</sub>)aryl group) (substitution selected from halo, (Cj-C<sub>2</sub>)alkyx, (Cj-C<sub>2</sub>)alkoxy group; C<sub>2</sub>-aryloxy group selected from phenoxy or substituted phenoxy, (substitution selected from halo, (Cj-C<sub>2</sub>)alkyl); (Cj-C<sub>2</sub>)alkyl

R\* is selected from hydrogen; (C1-C2)alkyl group selected from methyl or ethyl; amino; monosubstituted amino selected from straight or branched (C1-C6)alkylamino, cyclopropylamino, cyclobutylamino, benzylamino or phenylamino; disubstituted amino selected from dimethylamino, diethylamino, ethyl(1-methylethyl)amino, monomethylbenzylamino, piperidinyl, morpholinyl, 1-imidazolyl, 1-pyrrolyl or 1-(1,2,3-triazolyl); ( $C_6$ - $C_{10}$ )aryl group selected from phenyl,  $\alpha$ -naphthyl or  $\beta$ naphthyl; substituted (C6-C10)aryl group, (substitution selected from halo, (C1-C4)alkoxy, nitro, amino, (C1-C4)alkoxycarbonyl); acyloxy or haloacyloxy group selected from acetyl, propionyl or chloroacetyl; (C1-C4)alkoxy group; RaRbamino(C1-C4)alkoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or  $R^{a}R^{b}$  is  $(CH_{2})_{n}$ , n = 2-6, or  $-(CH_{2})_{2}W(CH_{2})_{2}$ - wherein W is selected from  $-N(C_{1}-C_{3})$  alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C1-C3)alkyl], O or S; or R3Rbaminoxy group, wherein RaRb is a straight or branched (C1-C4)alkyl selected from methyl, ethyl, n-propyl, 1methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl or RaRb is (CH2)n, n = 2-6, or -(CH2)2W-(CH2)2wherein W is selected from -N(C1-C3)alkyl [straight or branched], -NH, -NOB [B is selected from hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl], O or S; halo (C<sub>1</sub>-C<sub>3</sub>)alkyl group; (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonylamino group selected from tert-butoxycarbonylamino, allyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino or propoxycarbonylamino:

and when R =  $H^{\alpha}(CH_{\lambda}, SO_2$ - and n = 0,  $R^{\alpha}$  is selected from straight or branched  $(C_1-C_2)$ alkyl group selected from methyl or ethyl;  $(C_4-C_{10})$ aryl group selected from phenyl, e-naphthyl or  $\beta$ -naphthyl; substituted  $(C_4-C_1)$ aryl group, (substitution selected from halo,  $(C_1-C_4)$ alkoxy, nitro,  $(C_1-C_4)$ alkoxycarbonyl); a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, or S heteroatom optionally having a benzo or pyrido ring fused thereto:

Z = N, O or S

or a five membered aromatic ring with two N, O, or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

 $Z \text{ or } Z^1 = N, O \text{ or } S$ ;

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and when  $R = R^4 (CH_2)_n SO_2$  and n = 1-4,

- 10 R<sup>4</sup> is selected from hydrogen, straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl or ethyl; R<sup>5</sup> is selected from hydrogen, straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, ngroyl or 1-methylethyl;
  - R<sup>6</sup> is selected from hydrogen; straight or branched (C<sub>1</sub>-C<sub>2</sub>)alkyl group selected from methyl, ethyl, npropyl or 1-methylethyl; with the proviso that R<sup>5</sup> and R<sup>6</sup> cannot both be hydrogen;
- or R<sup>5</sup> and R<sup>6</sup> taken together are -(CH<sub>2</sub>)<sub>2</sub>W(CH<sub>2</sub>)<sub>2</sub>-, wherein W is selected from (CH<sub>2</sub>)<sub>n</sub> and n=0-1, -NH, -N(C<sub>1</sub>-C<sub>3</sub>)<sub>3</sub>klyf) (straight or branchad), -N(C<sub>1</sub>-C<sub>3</sub>)<sub>3</sub>kloxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.
- 20 11. The compound according to Claim 1, [4S-(4a.12aa)]-4.7-Bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,1,1,2e-octahydro-3,10,12,2e-letrahydro-y,11-dicxoz-2-aphthacencearboxamide; [4S-(4a,12aa)]-4.7-Bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-12ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2ab,1-2

tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate; [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-

- 25 naphthacenecarboxamide monchydrochloride; [4S-(4a, 12a)]-9-(Acetylamino)-4, 7-bis(dimethylamino)-1, 4-a5, 5a,6,11,12a-octahydro-3, 10,12,12a-tertahydro-y-1,1-id-oxo-2-naphthacenecarboxamide; [4S-(4a, 12a)]-4,7-Bis(dimethylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tertahydroxy-1,11-dioxo-9-(trifluoroacetyl)amino)-2-naphthacenecarboxamide sulfate; [4S-(4a, 12a)]-7-(Diethylamino)-4,0-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tertahydroxy-1,11-dioxo-2-naphthacenecarboxamidesulfate (1,2); [4S-(4a, 12a)]-9-(Acetylamino)-7-(diethylamino)-1,4-(a5,5a,6,11,12a-octahydro-3,10,12,12a-tertahydroxy-1,11-dioxo-2-naphthacenecarboxamidesulfate), 11-dioxo-2-naphthacenecarboxamidesulfate
  - (dimethylamino)-1.4. 4a,55a,6.11,12a-octahydro-3,10,12,12a-tetrahydroxy-1. 11-dioxo-2-naphthacenecarboxamide sulfate (1.2). [46-(4d.12ae)]-7-(0livhylamino)-4-(dimethylamino)-19-(formylamino)-1.4-4a,55a,6,11,12a-octahydro-3,10,12 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4d.12ae)]-9-(Acetylamino)-7-(diethylamino)-4-(dimethylamino)-1,4,a5,5sa,6,11,12a-octahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4d.12ae)]-4-(Dimethylamino)-9-3,101,212-eterahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4d.12ae)]-4-(Dimethylamino)-9-
  - (dormylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-lodo-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4-,12a-)]-4-(Dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-lodo-1,11-dioxo-2-naphthacenecarboxamide sulfate; [4S-(4a,12a-)]-4,7-Eisic(imiethylamino) -1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-f-(methoxyacetylamino)-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4a,12a-)]-9-f(4e-front-1-oxobutyl)
- amino]-4.7-bis(dimethylamino)-1.4.4a.5.5a.6,11,12a-octahydro-3,10,12.12a-letrahydroxy-1,11-dioxo-2-naphthacene-carboxamide; (4s-(4a.12aa))+4.7-Bis(dimethylamino)-1,4.4a.5.5a.6,1.1,12a-octahydro-3,10,1212a-letrahydroxy-1,11-dioxo-9<math>(1-oxo-2-propeny))amino]-2-naphthacene-carboxamide; (4s-(4a.12aa))-9-[((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Acetyloxy))-((Ace
- 36 3,10,12,12a-totralydroxy-1,11-dioxo-2-naphthaconocarboxamide sulfate: [45-(4a,12a-)-]0-(Benzoylamino)-4,7-bis(dimethylamino)-1,4-a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-11-dioxo-2-naphthaconecarboxamide; [45-(4alpha,12alpha)]-4,7-Bis (dimethylamino)-1,4-a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-9-(4-methoxybenzoylamino)-1,11-a|oixo-2-naphthaconecarboxamide; 145-4dalpha,12alpha)-1,7-Bis(dimethylamino)-1,4-a,5,5a,6,11,12a-octahydro-3,10,12,12a-bray-1,2alpha)-1,3-bis(dimethylamino)-1,4-a,5,5a,6,1,112a-octahydro-3,10,12,12a-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bray-1,3-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a)-bis(1-a
- tetrahydroxy-9-{(2-methylbenzoyl)amino)-1. 11-dioxo-2-naphthacenecarboxamide; [4S-(4alpha, 12aalpha))-4,7-Bis(dimethylamino)-9-{(2-fluorobenzoyl) amino)-1,4,4-8,5,5.a.6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,1-dioxo-2-naphthacenecarboxamide; {di-(4alpha, 12aalpha)+4,7-Bis-(dimethylamino)-1,4,4a, 5-5,a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-{(pentafluorobenzoyl)-amino)-1,1-dioxo-2-naphthacenecarboxamide hydrochloride; {di-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-Bis-(4alpha,12aalpha)+4,7-B
  - (dimethylamino)-1.4,4a,5,5a,6,11,12a-octahydro-3,10. 12,12a-tetrahydroxy-1,11-dioxo-9-[[3-(thfluoromethyl) benzoyljamino]-2-naphthacenecarboxamide; [45-(4alpha, 12aalpha]]-4,7-Bis-(dimethylamino)-9-[(2-furanylicarbonyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [45-(4alpha, 12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [45-(4alpha, 12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-octahydro-3,10,12,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10,12a-octahydro-3,10

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5.5a.6.11.12a-octahydro-3.10.12.12a-tetrahydroxy1,11-dioxo-9-[(2-thienylcarbonyl)amino]-2-
           nanhthacenerarboxamide:
                                                  [4S-(4alpha,12aalpha)]-4.7-Bis(dimethylamino)-1,4.4a,5.5a,6.11,12a-octahy
           dro-3.10.12.12a-tetrahydroxy-9-[(4-nitrobenzoyl)amino]-1,11-dioxo-2-naphthacenecarboxamide;
           (4α,12aα)]-9-[(4-Aminobenzoyl)amino]-4,7-bis-dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
           3.10.12.12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamidesulfate;
                                                                                                                       [4S-(4\alpha,12a\alpha)]-4,7-Bis-
           (dimethylamino)-9-[[(4-dimethylamino)benzoyl]amino]-1,4,
                                                                                                 4a.5.5a.6.11.12a-octahydro-3.10.12.12a-
           tetrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide; [7S-(7a,10aa)]-[2-[[9-(Aminocarbonyl)-4,7-bis-
           (dimethylamino)-5.5a.6.6a. 7.10.10a.12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
           amino]-2-oxoethyl]carbamic acid 1,1-dimethylethyl ester; [4S-(4\alpha,12a\alpha)]-9-[(Aminoacetyl)amino]-4,7-bis-
10
           (dimethylamino)-1.4.4a.5.5a.6.11.12a-octahydro-3.10.12.12a-tetrahydroxy-1.11-dioxo-2-
           naphthacenecarboxamide mono(trifluoroacetate); [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6.
           11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(phenylsulfonyl)amino]-2-
           naphthacenecarboxamide:
                                                  [4S-(4a,12aa)]-9-[[(4-Chlorophenyl)sulfonyl]amino]-4,7-bis(dimethylamino)-
           1.4.4a.5.5a.6.11.12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
                                                                                                                       [4S-(4\alpha,12a\alpha)]-4,7-Bis-
15
           (dimethylamino)-1,4,4a,5,
                                                  5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[(3-nitrophenyl)sulfonyl]-
           amino-1.11-dioxo-2-naphthacenecaboxamide; [4S-(4a,12aa)]-4,7-Bis(dimethylamino)-1,4,4a, 5a,6,11,12a-
           octahydro-3,10,12,12a-tetrahydroxy-9-[[(4-nitrophenyl)sulfonyl]amino]-1,11-dioxo-2-
           naphthacenecarboxamide:
                                                         [4S-(4x,12ax)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
           3.10.12.12a-tetrahydroxy-1.11-dioxo-9-[(2-thienylsulfonyl)amino]-2-naphthacenecarboxamide;
20
           (4a,12aa)]-9[[(2-(Acetylamino)-4-methyl-5-thiazolylsulfonyl]amino]-4,7-bis(dimethylamino)-
           1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-
           (4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[(ethylsulfonyl)amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,
           12.12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamide; [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-9-
           (formylamino)-1,4,4a,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-
           pyrrolidinylmethyl)-2-naphthacenecarboxamide;
                                                                                      [4S-(4\alpha,12a\alpha)]-4,7-Bis(dimethylamino)
           1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[(methanesulfonyl)amino]-1,11-dioxo-2-
           naphthacenecarboxamide; [4S-(4α,12aα)]-4,7-Bis(dimethylamino) -1,4,4a,5,5a,6,11,12a-octahydro-
           3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(phenylmethoxy)acetyl]amino]-2-naphthacenecarboxamide; [7S-
           (7\alpha,10a\alpha)]-[[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,10a,11-a,1
           tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]oxoacetic acid ethyl ester; [4S-(4\alpha, 12a\alpha)]-4,7-Bis-
           (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[(hydroxyacetyl)amino]-1,
           11-dioxo-2-naphthacenecarboxamide; [4S-(4a, 12aa)]-4,7-Bis(dimethylamino)-9-[[(methylamino)acetyl]-
           amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboximide
                                         [4S-(4a, 12aa)]-4-(Dimethylamino)-9-(acetylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
           hydrochloride:
           3,10,12,12a-tetrahydroxy-7-iodo-1,11-dioxo-2-naphthacenecarboxamide
                                                                                                             sulfate:
                                                                                                                               [7S(7a,10aa)]-[9-
35
           (Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-
           dioxo-2-naphthacenyl|carbamic acid methyl ester; [7S-(7a,10aa)]-[9-(Aminocarbonyl)-4, 7-bis-
           (dimethylamino)-5.5a.6.6a.7.10.10a.12-octahydro-1, 8.10a.11-tetrahydroxy-10.12-dioxo-2-naphthacenyl}-
           carbamic acid (2-diethylamino)ethyl ester; [7S-(7a,10aa)][9-(Aminocarbonyl)-4,7-bis(dimethylamino)-
           5,5a,6,6a,7, 10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid
                                            [7S-(7a,10aa)]-[9-(Aminocarbonyl)4,7-Dis(dimethylamino)-5,5a,6,6a,7,10,10a,12-
           octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid 2-propenyl ester; [4S-
           (4α,12aα)]-4.7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,
                                                                                                                             11,12a-octahydro-
           3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
                                                                                                       sulfate:
                                                                                                                       [4S-(4\alpha,12a\alpha)]-4,7-Bis-
           (dimethylamino)-1.4.4a.5.5a.6.11.12a-octahydro-3.10.12.
                                                                                          12a-tetrahydroxy-9-[(methoxyacetyl)amino}-
           1.11-dioxo-2-naphthacenecarboxamide hydrochloride; [4S-(4\alpha,12a\alpha)]-9-[(4-Bromo-1-oxobutyl)amino]-
           4,7-bis(dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1, 11-dioxo-2-naph-
           thacenecarboxamide sulfate: [4S-(4a, 12aa)]-9-[[(Acetyloxy)acetyl]amino]-4,7-bis(dimethylamino)-
           1.4.4a,5.5a,6.11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
           (4α,12aα)]-9-(Benzoylamino)-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
50
           tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
                                                                                         sulfate;
                                                                                                            [4S-(4alpha,12aalpha)]-4,7-Bis-
                                                                5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[3-
           (dimethylamino)-1,4,4a,5,
           (trifluoromethyl)benzovl]amino]-2-naphthacenecarboxamide
                                                                                                hydrochloride;
                                                                                                                          [4S-(4a,12aa)]-9-[(4-
           Aminobenzoyl)amino]-4,7-bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
           1, 11-dioxo-2-naphthacenecarboxamide; [4S-(4a,12aa)]-4, 7-Bis(dimethylamino)-9-[[(4-dimethylamino)-
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8.10a.11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-2-

benzoy]]amino]-1.4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride; [7S-(7a,10aa)]-[2-[[9-(Aminocarbonyl)-4, 7-bis(dimethylamino)-

5,5a,6,6a,7,10,10a,12-octahydro-1,

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oxoethyl]carbarnic acid 1.1-dimethylethyl ester hydrochloride; [4S-(4a,12aa]-9-[(Aminoacetyl)amino]-4,
7-bis-dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,
                                                           10,12,12a-tetrahydroxy-1,11-dioxo-2-naph-
                               [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[(ethylsulfonyl)amino]-
thacenecarboxamide:
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydro-
                     [4S-(4α,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-9-[(methanesulfonyl)amino]-1,11-dioxo-2-naphthacenecarboxamide sulfate; [4S-(4a,12aa)]-
4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,
                                                                    12a-tetrahydroxy-1,11-dioxo-9-[[-
(phenylmethoxy)acetyl lamino 1-2-naphthacenecarboxamide
                                                            hydrochloride;
                                                                              [4S-(4\alpha,12a\alpha)]-4,7-Bis-
                               6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[(hydroxyacetyl)amino]-
(dimethylamino)-1.4,4a,5,5a,
1.11-dioxo-2-naphthacenecarboxamide
                                         sulfate:
                                                    [4S-(4a,12aa)]-4-(Dimethylamino)-9-(acetylamino)-
1.4.4a.5.5a.6.11.12a-octahydro-3,10.12, 12a-tetrahydroxy-7-iodo-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4a,12aa)]-4,7-Bis(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-
3.10.12.12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamide; [7S-(7α,10aα)]-[9-(Aminocarbonyl)-4,7-
bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,
                                                                   10a,11-tetrahydroxy-10,12-dioxo-2-
naphthacenyl]carbamic acid methyl ester sulfate; [7S-(7α,10aα)]-[9-(Aminocarbonyl)-4,7-bis-
(dimethylamino)-5.5a,6.6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
carbamic acid (2-diethylamino)ethyl ester hydrochloride; [7S-(7a,10aa)]-[9-(Aminocarbonyl)-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8, 10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
carbamic acid ethenyl ester sulfate; [7S-(7α,10aα)]-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-
5.5a.6.6a.7.10.10a.12-octahydro-1.8.10a.11-tetrahydroxy-10.12-dioxo-2-naphthacenyllcarbamic acid 2-
propenyl ester hydrochloride; [4S-(4x,12ax]-4,7-Bis(dimethylamino)-9-[[(diethylamino) acetyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate;
[4S(4g,12ag1-4,7-Bis(dimethylamino)-9-[[(diethylamino)acetyl]amino]-1,4,4a,5,5a,6,†1,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride; [4S-(4a,12aa]-4,7-Bis-
                                                                  5a,6,11,12a-octahydro-3,10,12,12a-
(dimethylamino)-9-(f(diethylamino)acetyllamino]-1,4,4a,5,
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[-
(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide dihydrochloride; [4S-(4a,12aa)]-4,7-Bis(dimethylamino)-9-(chloroacetylamino)-
1.4.4a.5.5a.6.11.12a-octahydro-3, 10.12.12a-tetrahydroxy-1.11-dioxo-2-naphthacenecarboxamide; [4S-
(4alpha,12aalpha)]-9-[(Chloroacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride; [4S-(4alpha,12aalpha)-
]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4.4a.5.
                                                                  5a.6.11.12a-octahydro-3.10.12.12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
                                                      dihydrochloride;
                                                                          [4S-(4alpha,12aalpha)]-9-[-
(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-2-naphthacenecarboxamide (free base); [4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,7-
                                           12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naph-
bis(dimethylamino)-1,4,4a,5,5a,6,11,
thacenecarboxamide monohydrobromide: (4S-(4alpha, 12aalpha)I-9-[(2-Bromo-1-oxopropyl)amino]-4,7-
                                                                 12a-tetrahydroxy-1,11-dioxo-2-naph-
bis(dimethylamino)-1.4.4a,5.5a,6.11.12a-octahydro-3.10,12,
thacenecarboxamide hydrobromide; [4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-4,7-bis-
(dimethylamino)-1.4.4a,5.5a,6.11, 12a-octahydro-3.10.12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecar-
boxamide hydrobromide; [4S-(4alpha, 12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11, 12a-
octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-2-
naphthacenecarboxamide
                            dihydrochloride;
                                               [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
4-morpholineacetamide dihydrochloride; [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(ethylamino)-
acetyllamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide dihydrochloride; [4S-(4alpha, 12aalpha)]-9-[[(Cyclopropylamino)acetyl]amino]-
4.7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12aoctahydro-3,10,12,
                                                                 12a-tetrahydroxy-1,11-dioxo-2-naph-
thacenecarboxamide dihydrochloride; [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(butylamino)-
acetyl]amino]-1,4,4a,5,5a,6,
                                              11.12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide dihydrochloride; [4S-(4alpha, 12aalpha)]-9-[[(Diethylamino)acetyl]amino]-4,7-
bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,
                                                                 12a-tetrahvdroxy-1,11-dioxo-2-naph-
thacenecarboxamide
                          dihydrochloride;
                                                 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
                           dihydrochloride:
                                                [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,
1-pyrrolidineacetamide
5.5a,6.11,12a-octahydro-3,10,t2,12a-tetrahydroxy-9-[[[(2-methylpropyl)amino]acetyl]amino]-1,11-dioxo-
2-naphthacenecarboxamide dihydrochloride; [7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-
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(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-

1-piperidineacetamide dihydrochloride: [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-(dimethylamino)-5.5a,6.6a,7,10, 10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl}-1H-imidazole-1-acetamide dihydrochloride; [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1.4.4a.5.5a.6.11.12a-octahydro-3.10.12.12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[naphthacenecarboxamide dihydrochloride; (dimethylamino)acetyllamino1-1.4. 4a.5.5a.6.11.12a-octahydro-3.10.12,12a-tetrahydroxy-1, 11-dioxo-2naphthacenecarboxamide; [4S-(4alpha, 12aalpha)]-4,7-Bis(dimethylamino)-9-[[(hexylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide [4S-(4alpha,12aalpha)]-4.7-Bis(dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1, 11-dioxo-2-napthacenecarboxamide dihydrochloride; [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3.10.12.12a-tetrahydroxy-9-[[2-(methylamino)-1-oxopropyl]amino]-1,11-dioxo-2naphthacenecarboxamide dihydrochloride; [7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-(dimethylamino)-5.5a.6.6a.7.10.10a.12-octahydro-1,8.10a.11-tetrahydroxy-10.12-dioxo-2-naphthacenyl alpha-methyl-1-pyrrolidineacetamide dihydrochloride; [4S-(4alpha, 12aalpha)]-4,7-Bis(dimethylamino)-9-[[4-(dimethylamino)-1-oxobutyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11dioxo-2-napthacenecarboxamide dihydrochloride; [4S-(4alpha,12aalpha)]-9-[[(Butylmethylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)dihydrochloride; naphthacenecarboxamide 1.4.4a.5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2naphthacenecarboxamide dihydrochloride; [4S-(4alpha. 12aalpha) 1-4,7-Bis(dimethylamino)- $1,\!4,\!4a,\!5,\!5a,\!6,\!11,\!12a\text{-}octahydro-3,\!10,\!12,\!12a\text{-}tetrahydroxy-1,\!11-dioxo-9-[[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl]-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,\!11-dioxo-9-[[(phenylmethyl)amino]acetyl-1,$ amino]-2-naphthacenecarboxamide dihydrochloride; [7S-(7alpha,10aalpha)]-N-[2-[(9-(Aminocarbonyl)-10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-4,7-bis(dimethylamino)-5,5a,6,6a,7, naphthacenyl]amino]-2-oxoethyl]glycine; [4S-(4alpha, 12aalpha}}-4.7-Bis(dimethylamino)-9-[[-(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12, 12a-tetrahydroxy-1,11-dioxo-N-(1pyrrolidinylmethyl)-2-naphthacenecarboxamide; [4S-(4alpha, 12aalpha)]-4,7-Bis(dimethylamino)-9-[[-(dimethylamino)acetyl]amino]-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1, 11-dioxo-N-(4-morpholinylmethyl)-2-naphthacenecarbox amide; [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[-(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1piperidinylmethyl)-2-naphthacenecarboxamide; [7S-(7alpha, 10aalpha)]-N-[9-(Aminocarbonyl-4,7-bis-(dimethylamino)-5.5a.6.6a.7.10.10a.12-octahydro-1.8.10a.11-tetrahydroxy-10.12-dioxo-2-napthacenyl]-1azetidineacetamide; [4S-(4alpha,12aalpha)]-9-[[(Cyclobutylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

12. A compound according to Claim 6, [4S-(4-,12a-)]-4-(Dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-nitro-1,11-dioxo-2-naphthacenecarboxamide

13. A method of producing a compound of the formula:

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according to Claim 1, wherein X = NR<sup>1</sup>R<sup>2</sup>, which comprises reacting a 9-amino-7-(substituted amino)-6-demethyl-6-deoxytetracyclineof the formula:

with an acyl halide of the formula R-halide, an acylanhydride of the formula R-anhydride, a mixed acyl anhydride of the formula R-anhydride, a sulfonyl halide of the formula R-halide, or a sulfonyl anhydride of the formula R-anhydride in the presence of a sulfable acid scavenger in a sulfable solven.

# 15 14. A method of producing a compound of the formula:

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according to Claim 1, wherein X is a halogen, which comprises reacting a 9-(acyl or sulfonylamino)-6-demethyl-6-deoxytetracycline of the formula:

with a halogenating agent.

### 15. A method of producing a compound of the formula:

according to Claim 6, which comprises reacting a 9-(acyl or sulfonylamino)-6-demethyl-6-deoxytetracycline of the formula:

with a metal nitrate and a strong acid.

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16. A method of producing a compound of the formula:

according to Claim 6, which comprises reacting a compound of the formula:

with nitric acid and a strong acid.

17. A method of producing a compound of the formula:

according to Claim 1, wherein X = NR1R2, which comprises reacting a compound of the formula:

according to Claim 6 with the appropriate  $(C_1 - C_4)$  straight or branched aldehyde or ketone in the presence of an acid and hydrogen.

18. A method of producing a compound of the formula:

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according to Claim 1, wherein X = NR¹R² or halogen, which comprises reacting a 9-(substituted amino)-7-(halo or substituted amino)-6-demethyl-6-deoxytetracycline of the formula:

according to Claim 1 with a primary or secondary amine in the presence of formaldehyde.

- A method for the prevention, treatment or control of bacterial infections in warm-blooded animals which comprises administering to said animal a pharmacologically effective amount of a compound according to Claim 1.
- 20. A pharmaceutical composition of matter comprising a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.



# PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report Apparation (Village)

92 11 4281

DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document with indic of relevant passa	ation, where appropriate,	Relevant to chaim	CLASSIFICATION OF TH APPLICATION (Int. Cl. 5)
D, X	US-A-3 338 963 (JOSEP *Column1, formula; colu 41; examples26, 32-34 *	mn 4, lines 7 to	1,19,20	C07C237/26 C07D307/68 C07D333/38 C07D333/34
X	JOURNAL OF MEDICINAL vol. 6, no. 4, 9 July pages 405 - 407 JOHN L. SPENCER ET AL '6-deoxytetracyclines products' * the whole document:	1963, WASHINGTON US  V 7,9-disubstituted	1,19,20	C070277/36 C07D205/04 A61K31/16
^	US-A-3 579 579 (JOSEPI * the whole document	H J. HLAVKA ET AL)	1,19,20	
				TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
				C07C C07D
INCO	MPLETE SEARCH			
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-	Place of search	Date of completion of the words		Exemple 1 0
11	HE HAGUE	09 DECEMBER 1992	'	HENRY J.C.
X : parti	ATEGORY OF CITED DOCUMENTS cularly relevant if taken alone cularly relevant if combined with another	T : theory or principle E : earlier patent door after the filing du D : document cited in	iment, but public te	invention thed on, or



Claim searched incompletely: 19

Remark: Although claim 19 is directed to a method of treatment of the human/animal body (Article 52(4) EFC) the search has been carried out and based on the alleged effects of the compounds.

### INCOMPLETE SEARCH

Claims searched completely : 11,12 Claims searched incompletely : 1-10,13-20

Reason: As the drafting of the claims is not clear and concise and encompassed such an enormous amount of products a complete search is not possible on economic grounds. (See Guideline for examination in the EPO, part III,2) so that the search has been limited (Rule 45) to the examples.